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THE TREATMENT OF SYPHILIS

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THE TREATMENT OF SYPHILIS

BY

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TO MY BELOVED FATHER,
THE REVEREND OLIVER SHERMAN BAKETEL, D.D.
WHOSE SAINTLY LIFE HAS BEEN AN ABIDING SOURCE OF ADMIRATION, ENCOURAGEMENT AND DEVOTION, THIS BOOK IS AFFECTIONATELY DEDICATED

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PREFACE

To be successful in the treatment of syphilis, the physician must be the master of intravenous medication, for resultful treatment of lues is dependent to a very great extent on the administration of arsphenamine or neoarsphenamine.

The existing textbooks covering the field of syphilis, while strong in diagnosis and prognosis, are weak in that part of treatment which concerns the actual introduction of arsenical products into the system. They advise their employment but fail to give the readers in minutiæ the various steps by which a successful administration is accomplished. This fact is the raison d'être of this book.

It is not a volume for the skilled syphilographer, who has a technic which is entirely satisfactory to himself, but rather is intended for those physicians who have not heretofore employed the intravenous method of injection or those whose acquaintance therewith is limited. To some the elaborate detail of description as to the preparation and injection of salvarsan may appear elementary, but in that very fact lies its strength. A wide experience in the treatment of lues with the arsenicals and a comprehensive knowledge of this field of medical practice has demonstrated that many physicians are lacking in information as to the "whys, wheres and hows" of intravenous medication. It is for this great body of medical men who desire to treat intelligently and skillfully the luetic cases which come to their attention that this book has been written.

The author has drawn not only upon his own knowledge in its preparation but has also consulted the leading authorities on the disease. Credit has been given so far as known and we are indebted to many syphilographers and professional friends for advice and help.

Particular gratitude is expressed to Dr. John A. Fordyce and to Dr. Henry H. Morton for valuable suggestions and assistance,

as well as to Dr. Chester N. Myers, U. S. Public Health Service, and Dr. A. E. Sherndal for collaboration in the preparation of the chemistry of the arsenicals.

In carrying out the professional work on which the contents of this book are based, all brands of arsphenamine and neoarsphenamine have been utilized, including the German, American, English and Canadian, but the majority of the cases have been treated with salvarsan and neosalvarsan which seem to be the counterparts of the original products.

H. S. B.

16 Fifth Avenue, New York.

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THE TREATMENT OF SYPHILIS

THE TREATMENT OF SYPHILIS

CHAPTER I

THE PART OF THE WASSERMANN AND LANGE'S CHLORIDE OF GOLD TESTS IN THE DIAGNOSIS AND CONTROL OF THE VARIOUS FORMS OF LUETIC INFECTION

The Wassermann Reaction.—It is incomprehensible to think of treating a case of syphilis without the frequent utilization of the Wassermann test. While this test has been decried by certain individuals and while every careful observer will admit that it is not an infallible test, it would be out of the question in our opinion to treat lues successfully without its employment.

Throughout the pages of this book we show in the discussion of various matters of technic the occasion for employing the Wassermann reaction, because so far as we are able to determine it is an agent for the perfection of accuracy in diagnosis which is without an equal in the light of our present knowledge. Not only does it assist us diagnostically, but it also enables us to arrive more definitely at a prognosis.

It would be out of place in a treatise of this sort to go into the technic of the Wassermann reactions but, in view of its very great importance, it seems advisable to discuss a few of the terms that are being used in connection with the Wassermann. Reproduced herewith are extracts written by Drs. O. S. Hillman and A. M. Burgess for Mallory and Wright's excellent work on *Pathological Technique.* (W. B. Saunders Co., Philadelphia, 1918.)

Complement (Alexine).—"This is a substance which is found in all fresh sera; its activity is destroyed by exposure to heat at 55° or 56° C. for half an hour. Serum treated in this way is said to be inactivated, and can be reactivated by the addition of

another serum containing active complement. The sera of various animals differ in their complementary activity and also in their fixability, which is another characteristic that is possessed by complement. Anti-complementary action is a property which develops in a serum on standing or which may be present to a certain degree at the time the serum is drawn. In selecting a serum for the Wassermann reaction it is best to choose one which has the greatest degree of activity and fixability. It has been found that guinea-pig serum fulfills these demands probably better than the serum of any other species.

"**Amboceptor.**—This is a specific reaction product, which may be present in any normal serum, and which can be produced in the serum of an animal by repeated injections (immunization) of cells or substances (erythrocytes, serum, egg-albumin, etc.), for which it has no natural amboceptor. Amboceptors that are normally present in serum are called natural amboceptors; those which are produced as the result of artificial immunization are called immune amboceptors. Amboceptors are classified according to the particular substances employed in their production; for example, hemolytic amboceptors (also called hemolysins) are those that are produced by the injection of red blood-corpuscles into an animal; bacteriolytic amboceptors (bacteriolysins) are produced by the injection of bacterial extracts. An amboceptor is specifically defined by prefixing the term 'anti' to the name of the particular species employed in its production; for instance, when sheep's erythrocytes are the immunizing agent, the amboceptor is designated as an anti-sheep hemolytic amboceptor.

"Complement and amboceptor are the two factors necessary in the production of serum hemolysis. This can be demonstrated by a simple experiment, as follows: immunize a rabbit to human red blood-corpuscles by means of repeated injections, thereby producing in the rabbit serum an anti-human hemolytic amboceptor. If serum from such a rabbit is brought into contact with a suspension of washed human red blood-corpuscles, dissolution of the corpuscles or hemolysis will take place; if, however, the rabbit serum be heated to 56° C. for one-half hour (in-

activated), and then corpuscles added, no hemolysis will occur. Finally, if normal human serum or normal guinea-pig serum be added to the mixture, hemolysis will go on as before. These three factors which enter into this reaction, namely, the complement, the hemolytic amboceptor, and the red blood-corpuscles, constitute what is called, for the sake of brevity, the hemolytic system.

"The function of the amboceptor in the above reaction of hemolysis is to sensitize or prepare the erythrocytes for the action of the complement; the latter than has the power of causing dissolution of the red cells, resulting in a clear red fluid. Neither amboceptor nor complement acting alone can produce this result. For complete hemolysis a definite ratio must exist between the various factors—amboceptor, complement, and erythrocytes. The requisite strength and proportion of these three can readily be estimated by titration.

" **Antigens and Antibodies.**—Antigens are substances which, when injected into a suitable animal, are capable of producing in that animal substances called antibodies, the latter thus being specific reaction products. Erythrocytes, bacteria, and proteins are examples of antigens. Under antibodies are included hemolytic and bacteriolytic amboceptors, agglutinins, and precipitins. Antibodies are also found in the serum of patients suffering from infections with microörganisms. In typhoid fever, for instance, an antibody is developed in the patient's serum as a result of the action of the typhoid bacillus upon the immunizing mechanism of the body.

"Generally speaking, it may be stated that antigens and antibodies bear a specific relationship toward one another; for instance, the hemolytic amboceptor produced by injecting a rabbit with sheep's red blood-corpuscles acts with these corpuscles only and with no others. The agglutination of typhoid bacilli by the serum of the typhoid patient is also an example of this intimate connection between antigen and antibody; this fact is made practical use of in the Widal reaction for the determination of the typhoid agglutinin (antibody). The phenomenon of precipitation is another instance of the visible and direct action between

antigen and antibody. Both agglutination and precipitation are dual mechanisms requiring no intermediate agent to complete the reaction.

"In syphilis an antibody is supposed to be developed in the patient's serum, probably through the action of the treponema pallidum. It seems to be doubtful, so far as we know at present, whether the antibody in syphilis is actually specific or not. However, from a practical standpoint it may be said that it is the presence or absence of this so-called syphilitic antibody that we seek to demonstrate in the serum diagnosis of the disease.

" **Complement Fixation.**—As stated above, antigen and antibody unite with one another specifically, and, when united, acquire the property of fixing or absorbing complement. This fact can be best illustrated by the interaction of two sets of antigen-antibody combination. Take, for example, a suspension of typhoid bacilli (antigen) and bring it into contact with typhoid serum (antibody); if complement is now added, bacteriolysis will result. That complement has been fixed or absorbed by this antigen-antibody combination is evidenced by the fact that if red blood-corpuscles and their specific amboceptor (another antigen-antibody combination) be added later, no hemolysis will occur; complement, in other words, is not available for hemolysis on account of being fixed by the first antigen-antibody combination. This is the well-known phenomenon of complement fixation or deviation of Bordet and Gengou, upon which the Wassermann reaction and its various modifications are based. The so-called syphilitic antibody present in a patient's serum when brought into contact with an antigen is capable of fixing complement. This reaction is indicated by absence of hemolysis when the other two factors of the hemolytic system are added.

"When the reaction was first introduced, it was thought that the antigen used in the diagnosis of syphilis was specific, as it was then made from the liver of a syphilitic fetus. This was the nearest approach obtainable to actual extracts of the causative agent, namely, treponema pallidum. It has been conclusively proved that this original antigen is not specific, as it has been

found that extracts of normal livers, as well as other organs, and also certain lecithin preparations will fix complement in contact with not only luetic sera but also sera from patients infected with leprosy, yaws, sleeping-sickness, and malaria. The variability in the statistics of different writers is probably due to the variety of antigens employed, and at present this appears to be the principal limitation to the specificity of the reaction.

"The aqueous extract of the liver of a syphilitic fetus, which is used as an antigen in the original Wassermann reaction, is not employed in the following methods on account of its instability, and, incidentally, on account of the frequent difficulty of obtaining syphilitic fetuses. The modifications of the original test which have been devised depend, for the most part, on variations in the source of the antigen and in the employment of a different hemolytic system.

"Probably the most important modification is that of Noguchi, in which an antihuman hemolytic system is substituted for the antisheep and the acetone-insoluble fraction of an alcoholic extract of a normal organ (heart, liver, or kidney) is used as antigen. Plain alcoholic extracts of normal organs and of livers and spleens of syphilitic fetuses have been used by many workers in the Wassermann reaction, but at the present time the best antigen seems to be an alcoholic extract of human heart muscle saturated with cholesterin. On account of its stability for long periods, this antigen is particularly valuable, especially when reactions are done at infrequent intervals.

"For purposes of distinction the two following methods will be designated as the Wassermann and Noguchi reactions respectively, although, strictly speaking, the name Wassermann should be applied to the original method of doing the reaction—that is, with the aqueous extract of a liver of a syphilitic fetus.

"In the Wassermann reaction the patient's serum is inactivated in order to destroy the native complement, which is present, as a rule, in an appreciable amount. Complement of known strength necessary for the reaction is supplied by fresh guinea-pig serum. In the Noguchi reaction an antihuman hemolytic system is employed, as Noguchi maintains that, owing to the

presence in human serum of varying amounts of natural amboceptor for sheep's corpuscles, many positive reactions are rendered negative in the Wassermann test on account of an increase in the total amount of amboceptor present, thus disturbing the proper proportion between amboceptor and complement necessary for complete fixation. It is not necessary to inactivate the patient's serum in the Noguchi reaction, as the human complement is only very slightly hemolytic for corpuscles of the same species, and also because the amount of complement present is practically negligible, owing to the small quantity of patient's serum used for the test."

Dr. Archibald McNeil, director of laboratories of the National Pathological Laboratories, differs from the statement above that cholesterinated antigen is the best and most reliable one to employ. Such an antigen may at times give positive results in cases free from luetic infection, and, for this reason, Dr. McNeil believes that the plain alcoholic antigen is much safer and gives results that coincide more closely with clinical findings than does the cholesterinated antigen. The latter undoubtedly gives positive results in a number of latent and treated cases of lues in which the plain alcoholic extract antigen gives negative results. Dr. McNeil feels it would be better to obtain negative results in a positive case of lues than positive results in negative cases, especially as it is generally understood by the medical profession that a negative result does not exclude the possibility of luetic infection.

Very few practitioners are qualified by experience to make the Wassermann test, and those who are interested in it and desire the exact technic are referred to Mallory and Wright's book.

Lange's Colloidal Gold Test

They will find therein also a good description of Lange's colloidal gold test of the cerebrospinal fluid in syphilis. This test is easily and quickly made. "It consists," says Dr. John A. Fordyce (*Am. Jour. Med. Sci.*, October, 1916) " of a series of color changes which occur so characteristically and constantly that they may

be said to be specific. It is performed with ten dilutions of spinal fluid in geometrical progression from 1 to 10 to 1 to 5120. The color change depends on the amount of colloidal gold precipitated and varies from the negative salmon red through red blue, lilac or blue, blue gray or gray, and colorless. These changes may be plotted in curves or are arbitrarily expressed from zero to five. A negative colloidal gold would show no change and would therefore be expressed as 0000000000. In tabes and cerebrospinal syphilis the reaction occurs in the lower dilutions with the intensity of the change in the third and fourth or fourth and fifth tubes. The term 'luetic zone' or 'luetic curve' is used to describe this reaction. The reading would be as follows: 1133200000 or 1223320000. In meningitis of non-syphilitic origin the maximum change occurs beyond the syphilitic zone—that is, in the higher dilutions—while in paresis precipitation of the colloidal gold occurs regularly in the first four to eight tubes with decolorization or a turbidity, and the reading represented as 5555431000 or as many fives as there are decolorized tubes. To this zonal change Miller and Levy applied the term 'paretic curve.' A properly standardized—that is, a neutral solution of colloidal gold—shows either no change at all with a normal spinal fluid or produces a slight variation with a bluish nuance in the first four or five tubes which is negligible. Some cases may even give a change to a frank red blue in the first four tubes, so that the reading would be 1111000000, but with all the other laboratory findings negative it has been shown this had no diagnostic import.

"It may be said," continues Fordyce, " that, as a rule, there is a parallelism between the other positive findings in the fluid and a positive gold reaction. The significance of any one of the individual abnormalities must be appreciated before a proper interpretation can be placed upon the laboratory findings. We know that a lymphocytosis alone is not pathognomonic of syphilis as a mild grade is met with in other affections of the central nervous system and that the cell count cannot be relied upon to differentiate between tabes, cerebrospinal syphilis, and general paresis, as an equally high pleocytosis may be met with in any of

these conditions. So too the presence of globulin alone indicates organic disease of the brain or cord, but does not separate syphilitic from non-syphilitic disease.

"More positive information is derived from the complement-fixation test, as a positive Wassermann occurs only in lues. However, his test by itself does not supply a differential diagnosis as fixation to 0.2 c. c. or lower is met with not only in paresis but in some cases of progressive tabes and cerebrospinal syphilis. On the other hand, with a distinctly syphilitic process, as in cerebral endarteritis, abortive or stationary forms of tabes, and some types of cerebrospinal syphilis, the Wassermann may be completely negative. In the last-named cases a supplementary gold test is of value in demonstrating the luetic nature of the condition. Its greatest value and by far most prominent rôle, however, is in distinguishing between paresis and the conditions which simulate it as well as its prognostic significance in tabetics who show no mental impairment but give a paretic curve. Since the application of the gold sol test a number of patients in whom no cerebral involvement was suspected have given the curve characteristic of paresis."

Clinical Application of the Wassermann Reaction

This subject is so succinctly set forth by Dr. Henry H. Morton of Brooklyn in his admirable book (*Genito-Urinary Diseases & Syphilis*, p. 739, 1918, C. V. Mosby Co., St. Louis), that it is presented here *in toto:*

"The diagnostic value of the Wassermann test depends upon the fact that the antibody contained in the serum causing the reaction is specific, occurring only in the serum of luetics. Except in rare instances this has been found to be true. Positive reactions have been obtained in frambesia, relapsing fever, trypanosome infections, and tubercular leprosy. It is also found positive after veronal, morphin, scopolamin, ether narcosis (Wolfsohn), and frequently in sera obtained just before or after death. Therefore, while it is true that a positive reaction is obtained in a few diseases and conditions other than syphilis, the

differential diagnosis between syphilis and those diseases should not be difficult, at least in this country, and the reaction may be said to be practically specific.

"A negative reaction, on the other hand, can not be accepted as proof that the disease does not exist, as negative findings have been obtained in a small percentage of active cases of syphilis. If, however, a negative reaction is repeatedly obtained after several trials made at intervals, it is almost positive proof that the disease is not present. The reaction appears from two to four weeks after the appearance of the initial lesion, and persists throughout all stages of the disease unless influenced by treatment. A positive reaction has been obtained forty or fifty years after infection. Quite often a positive reaction may be obtained before the appearance of secondary symptoms. In the active stages of the disease 95 per cent of cases give a positive Wassermann reaction and at least 75 per cent of tertiary cases.

"In latent cases of the disease, while the continued existence of the spirochetæ renders the patients liable to outbreaks of symptoms at any time, nevertheless, the organism is often in a dormant state, which makes the appearance of symptoms less likely. In these latent cases a positive reaction is obtained in 50 per cent of the cases. It is in this class of cases that the Wassermann reaction is of special value as these patients are often apparently healthy and may give no history of ever having had the disease. Oftentimes a negative reaction in these latent cases may be transformed into a positive reaction by the administration of a short course of mercury or salvarsan."

CHAPTER II

ANTI LUETIC AGENTS

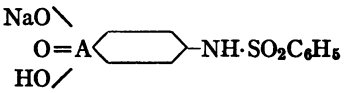
In the constitutional treatment of syphilis dependence is placed mainly on three drugs, arsenic, mercury, and iodin in the form of the iodides. The preparations mostly used are:

- **Arsenic**
  - Given by Intravenous, or Intramuscular, or Subcutaneous Injection or by rectum
    - Arsphenamine
    - Neoarsphenamine
- **Mercury**
  - Given orally
    - Protiodid
    - Bichlorid
    - Mercury with chalk
    - Biniodid
    - Calomel
    - Blue Mass
  - By Fumigation or Inhalation
    - Calomel
  - By Inunction
    - Oleate—10 per cent
    - Unguentum hydrargyri
  - By Hypodermic Injection in Gluteal Muscles
    - Soluble
      - Bichlorid
      - Succinimid
      - Biniodid
      - Benzoate
    - Insoluble
      - Salicylate
      - Calomel
      - Gray oil
- **Iodides**
  - Given By Hypodermic Injection By Enema or Intravenously
    - Potassium iodid
    - Sodium iodid
    - Ammonium iodid
    - Strontium iodid

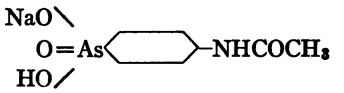
CHAPTER III

THE HISTORY AND CHEMISTRY OF ARSPHENAMINE

Before the knowledge of chemotherapy had reached its present stage, arsenic compounds had been used haphazardly for the cure or alleviation of syphilis and other protozoal diseases for many years, probably just as long as mercury. At first only inorganic arsenic derivatives were known, but with the extension in the field of preparative organic chemistry which occurred early in the 19th century, some organic combinations of arsenic became known which were used to some extent in therapy. The recent development in the use of arsenic compounds in medicine received its original impetus in the discovery of the curative action of atoxyl [1] on sleeping-sickness. The chemical structure of this substance, which was obtained by the action of arsenic acid on aniline, was first correctly explained in 1907, when Ehrlich demonstrated that it was the sodium salt of para-amido-phenyl arsinic acid.[2] The possibility of subjecting this substance to the chemical transformations characteristic of benzol derivatives was thus opened, and from then on attention was chiefly centered on such aromatic organic arsenic derivatives because of their comparatively low toxicity and apparent curative properties. In addition to atoxyl, "Hectine," a benzene sulfonate of atoxyl,[3]



"Arsacetin," an acetyl atoxyl,[4]



and "Asiphyl," a mercury salt,[5]

$$[NH_2 \cdot C_6H_4 \cdot AsO(OH).O]_2Hg$$

were proposed as therapeutic agents.

Affinity between Certain Living Cells and Chemical Substances.—The haphazard method of using these compounds stopped with the development of a definite theory of specific affinity between certain living cells and certain chemical substances, and its practical application to internal antisepsis for the cure of trypanosome and spirochætal diseases. Binz and Schulz [6] had found that arsenic acid was reduced in animal tissues to arsenious acid. It had also been noted that cacodylic acid was reduced in the organism. Ehrlich concluded from this that the arsenic compounds which had been used hitherto, and which were all derivatives of pentavalent arsenic, did not exercise an action on the parasites until after they had been reduced by the organism to the trivalent form.

Investigation along this line led to the greatest advance in the preparation of therapeutically valuable substances. It was found that by reducing the pentavalent compounds of arsenic to the trivalent form an enormous increase in the power to destroy the parasites which cause disease was developed. For example, para-oxy-phenyl arsinic acid does not kill trypanosomes in dilutions as strong as 1 or 2%, whereas if reduced to the corresponding trivalent arsenic compound, para-oxy-phenylarsenoxide, it kills trypanosomes quickly in dilutions of 1 to 10 million.[7]

Further investigation led Ehrlich to conclusions in regard to the mechanism of the action of these drugs on the parasites, which form the basis of the theory of arsenic chemotherapy as at present generally accepted. According to this theory the parasite possesses certain points of attack, termed by Ehrlich "chemoceptors" which have a specific affinity for certain chemical groups, of which trivalent arsenic is one. Other groups, such as the amido (NH_2), the hydroxyl (OH), appear to anchor themselves to definite parasites and so exert on them the specific drug action.

The Discovery of Salvarsan

By a combination of work in chemical synthesis and biological examination along the lines of this theory, covering many years,

Ehrlich and his co-workers arrived at a substance which has produced very remarkable therapeutic results. It was originally imported under the name "Salvarsan" and its manufacture in this country by Federal license under the name "Arsphenamine" has become an important factor in the industry of synthetic drugs. Several million ampules of arsphenamine and its compounds have been manufactured and distributed in this country, and the Government's campaign against venereal disease in which arsenicals of this type will play an important part, has still further increased the necessity of production on a large scale.

In the work which led to the preparation of salvarsan, the object sought after was a substance which would combine maximum toxicity to the disease-producing parasite with minimum toxicity to the organism which harbored the parasite. The measure of the former is the curative dose, of the latter the tolerated dose. The success in attaining this object may be judged by a comparison of the ratio of curative to tolerated dose in some of the better known arsenicals: atoxyl 1:2, arsacetin 1:3, arsenophenyglycine 1:2, salvarsan 1:58.[8]

Preparation of Arsphenamine

The preparation of arsphenamine involves a number of chemical processes in a field which is comparatively complicated and requires a large amount of special knowledge. It is further complicated by the necessity of extra precautions on account of the great susceptibility of the final product to chemical and physical influences. A great variety of methods for its production have been proposed but as might be expected the number of processes used for practical purposes is comparatively limited.

The first step in the synthesis of the aromatic organic arsenic compounds is the introduction of arsenic into the benzene nucleus. The methods which have been applied commercially for this purpose are probably limited to three.

1. The Bechamp condensation, melting arsenic acid with aniline to produce arsanilic acid,[9] or with phenol to produce para-oxy-phenyl arsinic acid.[10] The best yields are obtained

in the aniline melt. The process must be carefully regulated as to proportions of reagents and temperature, in order to obtain the best results. With high temperatures and an excess of aniline, the tendency to the formation of secondary arsanilic acid is increased.

With phenol the condensation appears to give less satisfactory yields, although as a step in the preparation of arsphenamine it has the advantage of leading more directly to the goal.

2. The arseniation of dimethylaniline with arsenic trichloride, leading to N-dimethyl arsanilic acid. This process appears to be used in connection with French patents for the manufacture of arsphenamine.[11]

3. Bart's reaction, coupling diazo compounds in alkaline solution with sodium arsenite. This method is capable of very wide application and starting from para-amido-acetanilide has been applied commercially to the production of arsanilic acid.[12] From the arsinic acids produced by these methods a large number of derivatives can be obtained, by the usual chemical reactions on benzene compounds. The practical production on a large scale of some of these requires considerable elaboration.

The Immediate Mother Substance of Arsphenamine

The immediate mother substance of arsphenamine is 3-nitro-4-hydroxy-phenylarsinic acid. A large number of procedures for the preparation of this substance have been proposed. One of the methods generally used starts from parahydroxy-phenyl arsinic acid, obtained by the action of arsenic acid on phenol, or by the diazotization and hydrolysis of arsanilic acid. This hydroxy acid is then nitrated at a low temperature to form the nitrohydroxy acid. Another method consists in combining arsanilic with oxalic acid, nitrating the resulting oxalyl compound, subsequent saponification and hydrolysis with strong caustic potash leading to the nitro-hydroxy acid which is used for conversion into arsphenamine.

The 3-nitro-4-hydroxy-phenyl arsinic acid used for the production of arsphenamine can and should be prepared in a high state

of purity. Arsphenamine itself cannot be purified, consequently all possible extraneous material should be eliminated, previous to the final step in the manufacture.

From 3-nitro-4-hydroxy-phenyl arsinic acid, the process of preparing arsphenamine consists in a reduction of the nitro to an amino group and a partial reduction of the arsenic acid group, forming a double bond between two molecules. The resulting insoluble arseno base is then isolated, converted into its soluble dihydrochloride, isolated by suitable precipitation, dried thoroughly in a high vacuum, and packed in ampules in vacuum or inert gas.

If the reduction is carried too far, highly toxic arsines may be formed, if the reduction is insufficient or improperly carried out, the nitro group may be left intact, or the arsenoxides formed. Several methods for the reduction and subsequent treatment have been proposed. The original scheme was a progressive reduction, first of the nitro group by means of sodium amalgam, then of the arsenic group by the action of sulfur dioxid in acid solution with potassium iodid as a catalyst.[13] Kahn patented a procedure involving a complete reduction to the primary arsine, which was then added to a solution of the amino-phenyl-arsenoxid with which it combined forming the arseno base.[14] The reduction by means of phosphorous or hypophosphorous acid has also been described [15] and the use of zinc dust, zinc chlorid and sulfurous acid has been subject of patents.[16]

For the practical purpose of large-scale production sodium hydrosulfite has probably been used exclusively, and under proper conditions has proven an ideal reagent, although it introduces the necessity of removing certain impurities from the crude arseno base. When this method is used the reduction takes place in one stage, and the arseno base, being insoluble in the medium, can be filtered directly.

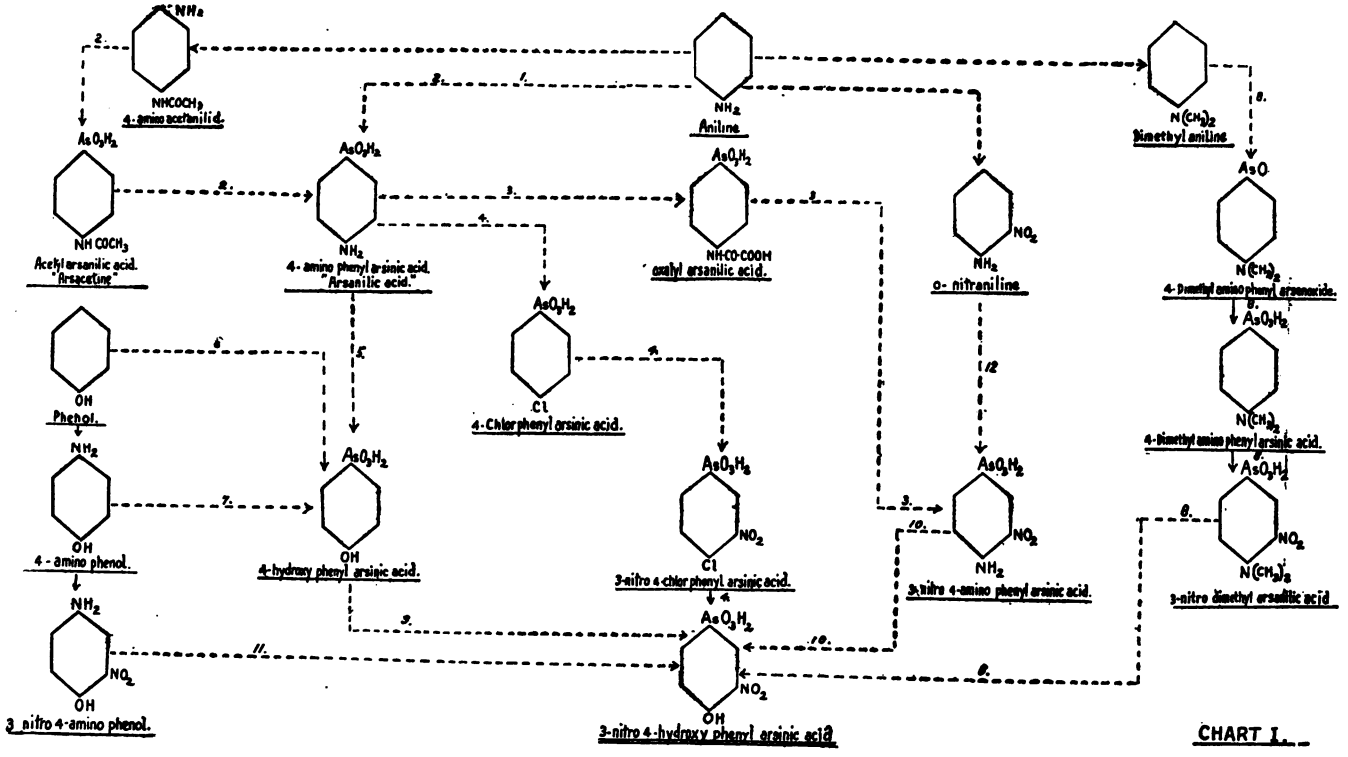
For the preparation of the dihydrochlorid, a method has been patented for the precipitation of a solution from hydrochloric acid.[17] The generally used procedure consists in dissolving the base in methyl-alcoholic hydrochloric acid and precipitation of the dihydrochloride by means of ether.[18]

In the final steps of the manufacture of arsphenamine it is important to exclude atmospheric oxygen. In the reduction by sodium hydrosulfite, this is taken care of by the sulfur-dioxid formed by the oxidation of the hydrosulfite. During the filtration of the base, the preparation of the dihydrochlorid and its final isolation, air should be replaced by carbon dioxid or other inert gas. To insure a product of maximum stability, it must be carefully dried in high vacuum, and all subsequent operations conducted in an atmosphere of inert gas.

There appears to be some doubt as to whether such careful precautions are really necessary and it is possible that a pure arsphenamine, particularly after moisture and solvents have been removed, is a very much more stable substance than appears from some of the literature on the subject. There is no doubt, however, that in view of the nature of the material and the use to which it is put, the best method of procedure is to adopt every possible precaution in the manufacture, even at the risk of overdoing it.

Explanatory Diagrammatic Outline

The large number of proposed chemical procedures for the preparation of arsphenamine and its intermediates is outlined in the following charts, which show the chemical relationship of the various substances to the final product, arsphenamine.


NH2
NHCOCH3
4-amino acetanilid.
Aniline
N(CH3)2
Dimethyl aniline
AsO3H2
NH COCH3
Acetyl arsanilic acid.
"Arsacetine"
NH2
4-amino phenyl arsinic acid.
"Arsanilic acid."
NH-CO-COOH
oxalyl arsanilic acid.
NO2
NH2
o-nitraniline
AsO
N(CH3)2
4-Dimethyl amino phenyl arsenoxide.
OH
Phenol.
Cl
4-Chlor phenyl arsinic acid.
N(CH3)2
4-dimethyl amino phenyl arsinic acid.
NH2
OH
4-amino phenol.
OH
4-hydroxy phenyl arsinic acid.
NO2
Cl
3-nitro 4-chlor phenyl arsinic acid.
NO2
NH2
3-nitro 4-amino phenyl arsinic acid.
NO2
N(CH3)2
3-nitro dimethyl arsanilic acid
NH2
NO2
OH
3 nitro 4-amino phenol.
NO2
OH
3-nitro 4-hydroxy phenyl arsinic acid
1.
2.
3.
4.
5.
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7.
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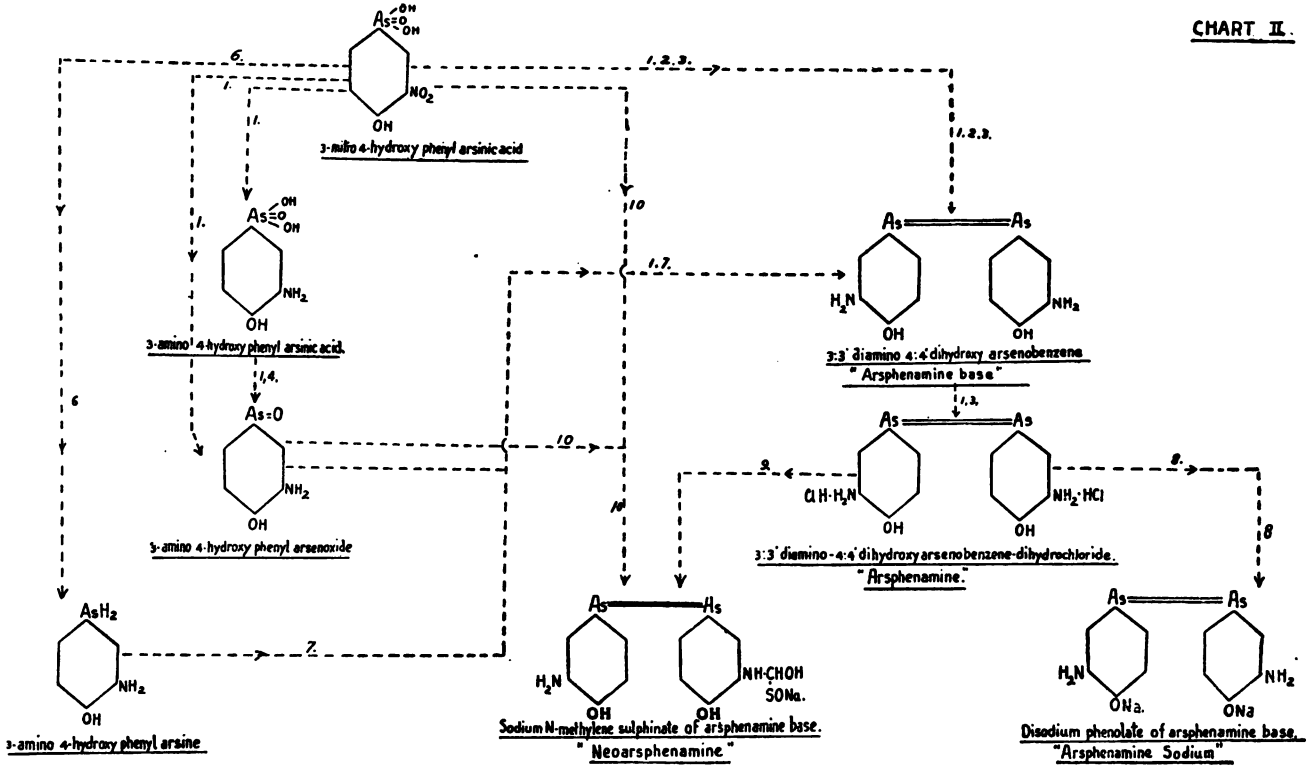
12.

CHART I.

CHART II.


3-nitro 4-hydroxy phenyl arsinic acid
3-amino 4-hydroxy phenyl arsinic acid.
3-amino 4-hydroxy phenyl arsenoxide
3-amino 4-hydroxy phenyl arsine
3:3' diamino 4:4' dihydroxy arsenobenzene
"Arsphenamine base"
3:3' diamino-4:4' dihydroxy arsenobenzene-dihydrochloride.
"Arsphenamine."
Sodium N-methylene sulphinate of arsphenamine base.
"Neoarsphenamine"
Disodium phenolate of arsphenamine base.
"Arsphenamine Sodium"

It would appear that every conceivable avenue of approach has been utilized for the preparation of arsphenamine. It is probable, however that only a few of these proposed methods have been applied to practical production of the material. The value of any single method can only be judged by extensive study and application to the production of material which is satisfactory chemically, therapeutically and economically.

The considerable physical and chemical variations in different brands of arsphenamine as now obtainable, indicate that the processes used by different manufacturers vary to some extent either in principle or method of manipulation. Color and solubility in solvents, particularly in methyl alcohol, and the ease with which the material forms aqueous solutions differ decidedly with different brands. The arsenic content varies from about 29 to about 33 per cent. Since the theoretical arsenic content of pure arsphenamine is 34.2 per cent, these figures represent great variations in purity and may affect the dosages used in biological tests and clinical practice by as much as 10 per cent. The impurities which produce this low arsenic content as far as at present known consist of moisture, various amounts of solvents, inorganic material, and sulfur. These variations in the product no doubt have an important bearing on variations in clinical results and the advantages of standardizing the preparation are obvious.

The Manufacture of Arsphenamine

At the present time most American manufacturers produce arsphenamine in comparatively small batches, of 500 or 1,000 grams, and a recently published English monograph on organic arsenicals notes with apparent satisfaction that batches of 1,500 grams are being produced. For quantity production this small scale involves the employment of many assistants, working in shifts, and an obvious possibility of insufficient control resulting in a lack of uniformity in the product. By calling to aid the mechanical means well known to the chemical engineer, so as to insure absolute and constant control throughout the process, it has been found possible to produce salvarsan in batches of over

7,000 ampules at a time. Careful comparisons have shown that the material manufactured on this scale is as good or better than can be obtained from small laboratory batches in which identical raw materials are used. The capacity of a plant operating on this basis is about 14,000 ampules of 0.6 gram every 14 to 16 hours. This large-scale production also has the advantage of insuring the absolute identity of a large amount of material, from which data can be obtained in regard to the influence of technic and personal factors on the results obtained from the administration. At the same time it gives the practitioner complete assurance as to the uniformity of a product should he desire to use many doses of one batch on a series of patients for purposes of comparative study. The product is uniform chemically, toxicologically and therapeutically. It is identical in every respect with the original preparation upon which the therapeutic reputation of the drug was established. It is tolerated by test animals in doses of 120 mg. and higher pro kilo body weight which represents a very low toxicity as compared with other drugs used in a similar manner.

A criticism of arsphenamine may be made on the ground of inconvenience in administration. The product occurs in the form of its dihydrochloride, which should be readily soluble in water of ordinary temperature. This solution is not suitable for injection, however, until the hydrochloric acid has been neutralized and the arsphenamine then further converted into its di-sodium salt. The addition of the improper amount of alkali for this purpose, either too much or too little, produces solutions which may give trouble in injection. If the arsphenamine requires hot or boiling water to form the solution, the preliminary preparation of the intravenous solution becomes still more complicated, and more possibilities of affecting the proper action of the drug are introduced.

The Evolution of Neoarsphenamine

With the idea of simplifying the technic of administration, modifications prepared from arsphenamine have been introduced which dissolve readily in water, forming solutions which

are ready for injection without further manipulation. Of these, neoarsphenamine is coming largely into favor, since in addition to its convenient administration it is also less toxic than arsphenamine. This substance is prepared from arsphenamine by combination with sodium formaldehyde sulfoxylate. It occurs in the form of its yellow sodium salt, readily soluble in water with slightly alkaline reaction. This product is being manufactured on a large scale in the United States and a very extended use in clinical practice has given satisfactory results.

The dry sodium salt of arsphenamine has also been proposed as a more convenient form for administration. This dissolves readily in water forming a solution which corresponds exactly to that obtained in the preparation of a properly alkalinized arsphenamine solution. It has been manufactured in this country, but does not appear to have come into any extended use.

A number of other arsenicals have been proposed as substitutes for or as improvements on arsphenamine. Since arsphenamine is a patented product and can only be manufactured under license, it is obvious that many attempts to introduce competitive products will be made. So far, no other arsenical has shown advantages which would enable it to replace or compete with arsphenamine to any marked degree.

The Precursors of Arsphenamine

During the work which culminated in the preparation of arsphenamine, a very large number of other arsenicals were synthesized and studied, some of which were for a time used in therapy. They may be considered as the precursors of arsphenamine, and the results of their use indicated the lines along which improvements might be effected. As already noted, atoxyl was the first of the extensively used aromatic organic arsenicals. This was replaced later by its acetic acid derivative under the name of arsacetine.

After Ehrlich took up the study of these arsenicals and discovered the decided increase in trypanocidal efficiency caused by their reduction to the trivalent arseno compounds, phenyl-

glycine-arsinic acid was introduced as No. 418 in his experimental series. Its sodium salt, under the name "spirarsyl" constituted an important advance over atoxyl and its immediate derivatives, and was the most successful remedy among the arsenicals which preceded salvarsan.

It was later replaced by salvarsan, No. 606, of Ehrlich's series, which represents the culminating point of this line of research. Attempts to simplify its use in therapeutics led to the introduction of neosalvarsan and salvarsan sodium which have already been described. The former is numbered 914 in Ehrlich's series.

Working along the same line and with a similar object in view, Mouneyrat prepared a phosphamic acid derivative of arsphenamine which was marketed under the name "Galyl" No. 1116, and subsequently a complex disulfonamide of arsphenamine appeared under the name "Ludyl," No. 1151 of Mouneyrat's series. These preparations both belong to the neoarsphenamine type of arsphenamine derivatives, intended to produce neutral or feebly alkaline solutions ready for injection without preliminary manipulation.

Other Arsphenamine Derivatives

Another type of arsphenamine derivatives which have received considerable attention are the co-ordination compounds with various metals. This interaction, discovered during Ehrlich's researches on salvarsan, appears to be a general one with organic arsenical compounds, although on account of their therapeutic importance it is chiefly the co-ordination compounds of arsphenamine which have been studied.

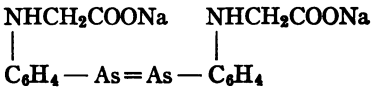
Danysz prepared co-ordination compounds of arsphenamine with silver salts, and introduced "Luargol" in which the action of the drug is reinforced by silver bromide and antimony oxide. A large number of other co-ordination compounds of arsphenamine and neoarsphenamine have been studied, in which salts of mercury, silver, gold, copper and platinum are in combination, but the preparations mentioned above are the only ones which have been used therapeutically to any extent. The same applies

to other modifications of the molecule, in which the various characteristic groups have been substituted or rearranged with a view to modifying or improving the therapeutic action.

It is not many years ago that the chemistry of the organic arsenic compounds occupied only a very modest place in chemical literature, but in recent years, the interest in their therapeutic application has developed a voluminous record of research and experiment along these lines, and several monographs on organic arsenicals have been published. The chemical structure of the arsenicals mentioned above is shown in the following cut, and also some of the modifications of arsphenamine which have been patented with the object of introduction as arsphenamine substitutes. They will indicate some of the lines along which attempts are being made to improve or replace the products which are now in use.

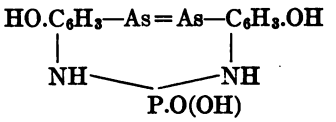
SPIRARSYL—sodium arsenophenylglycinate

No. 418 in Ehrich's series



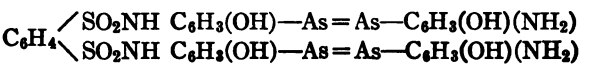
GALYL—dihydroxy-arsenobenzene-phosphamic acid

No. 1116 of Mouneyrat's series



LUDYL—benzene-disulphamino-bis-amino-dihydroxy arseno benzene

No. 1151 of Mouneyrat's series



LUARGOL.—diamino-dihydroxy arseno benzene-silver-bromide-antimonyl-sulfate.

No. 102 of Danysz series

$[(NH_2)(OH)C_6H_2—As=As—C_6H_2(OH)(NH_2)]_2$ Ag Br. SbO. $(H_2SO_4)_2$

Typical co-ordination compound;

Me denotes metal

X " halogen

AS . . . . . Me X
||
AS . . . . . Me X

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11. Poulenc and Oechslin, Fr. Pat. 449373, 451078, 474056.
12. Bart, D. R. P. 250264, Eng. Pat. 568 (1911).
13. Ehrlich and Bertheim, U. S. P. 986148.
    Benda and " Ber. 41, 1657 (1908).
    Ehrlich and " Ber. 45, 761 (1912).
14. D. R. P. 251571, 254187.
15. D. R. P. 271894, 206456.
16. Poulenc, Eng. Pat. 21421 (1914).
17. See 15, and also D. R. P. 216270, 235430, 269886, 269887.
    Kober J. A. C. S. (1919) 442.
18. Morgan, Organic Compounds of Arsenic and Antimony (1918), p. 226.
19. D. R. P. 206057; U. S. Pat. 888321 and 907016 (1908).
    Ehrlich, Ber. 42, 36 (1909).
20. Eng. Pat. 3087, and 9234 (1915).
21. Morgan, Organic Arsenic Compounds, p. 256.
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CHAPTER IV

THE CHEMOTHERAPY OF ARSENIC COMPOUNDS

The selective action of a compound for certain cells depends on the coming together of a particular group in the molecule into some sort of chemical connection with the cell substance. In 1898, Ehrlich (*Deut. med. Woch.*, page 1052) advocated the theory that the selective action of a compound for certain cells must be based upon the penetrability of the drug. This difference of affinity determined whether the drug had greater power to destroy the parasite or to combine with the protoplasm of the host. In the one case it is known as a parasitropic and in the other an organotropic substance. After many years of investigation of arsenic compounds, the field of arsenic therapy was divided into two sections. One was devoted to the study of arsenic in the pentavalent form, the other, to arsenic in the trivalent form.

There are at least three well-defined qualifications that a preparation must possess and they are summed up as follows:—

1. The compound must be non-irritant and capable of remaining in perfect solution at the temperature and the alkalinity of the tissues.

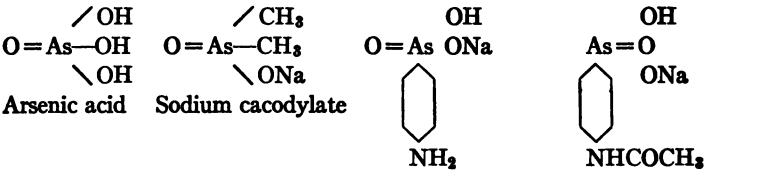
2. It must act quickly on the parasites before they can acquire a tolerance to the drug.

3. When the parasites have been expelled from the blood by therapeutic doses, there must be no recurrence in a majority of cases within some fixed time, which will depend to some extent on the particular host and the strain of parasites.

Pentavalent Arsenic Compounds

Along these lines of research much work has been carried out and certain arsenic compounds have been selected as partially fulfilling these requirements. In chemical language we have two groups of arsenic compounds, inorganic and organic. For use

in the present instance, only the organic compounds will be considered. We will deal first with the pentavalent arsenic preparations and then discuss the trivalent arsenic compounds. Arsenic has had some reputation in the treatment of protozoal diseases since the time of Fallopius. The compounds containing arsenic in the pentavalent condition are:—



Biological examination shows that all of these products are comparatively nontoxic when introduced into the animal system until changes take place that liberate arsenic. The arsenic in these compounds is liberated very slowly in the system, thus producing the ordinary therapeutic effects of the element. The chief objection to this class of compounds is found in the fact that they are excreted readily and generally in an unchanged form. This means that relatively large doses must be administered to gain beneficial results, while on the other hand the kidneys and liver are suffering from a tremendous oversupply of arsenic. Another objection is found in the fact that treatment with this class of compounds is followed by degeneration of the optic nerve and optic atrophy. These as well as the therapeutic action are mainly due to the reduction products which are formed in the organism.

Pentavalent arsenic probably produces cumulative effects after repeated doses. Atoxyl was found to be very efficient in trypanosomiasis but also it was found that in vitro there was little activity for the reason that there was no reduction of the arsenic to the trivalent condition. Röhl, and Friedberger (*Zeitschrif. Imunitäts forschung u. exp. Ther.*, Vol. I, 1909) *Berl. klin. Woch.* 1909, *No. 11*, *Berl. klin, Woch.*, 1908, *No. 38*, *Therap. Mon-*

ats, May, 1911) state that the curative action probably depends on the transformation of the organic pentavalent arsenic compounds into trivalent preparations which are directly toxic to protozoa in the same manner that arsenic pentoxid is partly reduced in the organism to arsenious acid. (Binz and Schulz, *Archiv. f. exp. Path u. Pharm.*, Vol. II, page 200, 1879.)

Furthermore, pentavalent compounds cause disturbances of the digestive system and nephritis as well as toxic effects on the general nervous system. When these compounds are administered continuously characteristic symptoms of arsenic poisoning are manifested. The pentavalent organic arsenic compounds do not produce any effect on trypanosomes in vitro whereas trivalent compounds, either organic or inorganic, show considerable activity. This difference of therapeutic action is probably due to the variability of chemical activity.

It seems to be a well-established fact that all arsenical combinations, which are capable of reacting chemically, are pharmacologically active, producing effects which in the last analysis are due to the action of the anions, AsO_3 or AsO_4. The action further might be explained in terms of energy changes in which the valency of the element changes from pentavalent to trivalent. A similar theory is found in the case of dyes in which there is a certain chromophore group in addition to an anchoring group or salt-forming group. This group is one in which nitrogen is involved and is well illustrated by the azo group—N=N—.

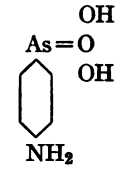
Why Pentavalent Compounds are Unsatisfactory

In conclusion the pentavalent arsenic compounds are unsatisfactory, due to the rapid excretion of the product and to the fact that the anatomic changes show degeneration of the optic nerve and retinal ganglia as well as the cerebral cell injury. Furthermore the curative dose is so close to the toxic dose that it renders most of these products dangerous, *i. e.*, the ratio of the curative dose to the tolerated dose is a small fraction. With a large dose for curative purposes it means an increased effort on the part of the kidneys and liver to withstand this attack. It should not be inferred that this class of compounds do not have any

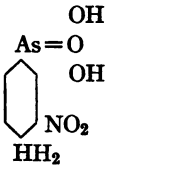
therapeutic action but it is a fact that in most cases they are less satisfactory than the compounds containing trivalent arsenic.

Trivalent Arsenic Compounds

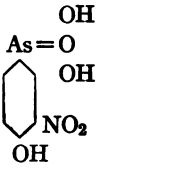
The trivalent compounds of arsenic are many in number but only a few has been of practical use inasmuch as the adaptability of many of them has not been entirely satisfactory. From this large number a few have been selected because the ratio between the etiotropic efficiency and the toxicity has been more favorable. In the case of salvarsan this ratio, according to the Hata method, was 1:58. Two products of this type have been used very extensively during the past ten years. However, this is no indication that other useful products cannot be obtained. A few structural formulas will indicate the organic preparations that illustrate trivalent arsenic in combination with ring compounds.



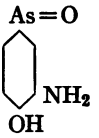
Arsanilic acid. pentavalent



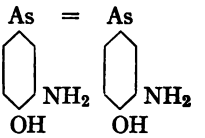
Nitro arsanilic acid. pentavalent



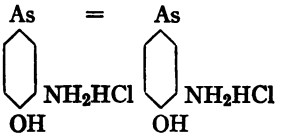
Nitro-oxy phenyl arsinic acid. pentavalent



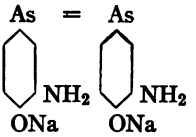
Amino oxy phenyl arsenoxide.
Twice as curative as salvarsan
6 times as toxic.
Trivalent arsenic



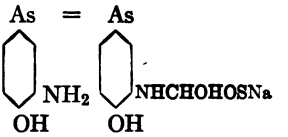
Salvarsan base
Trivalent arsenic



Salvarsan



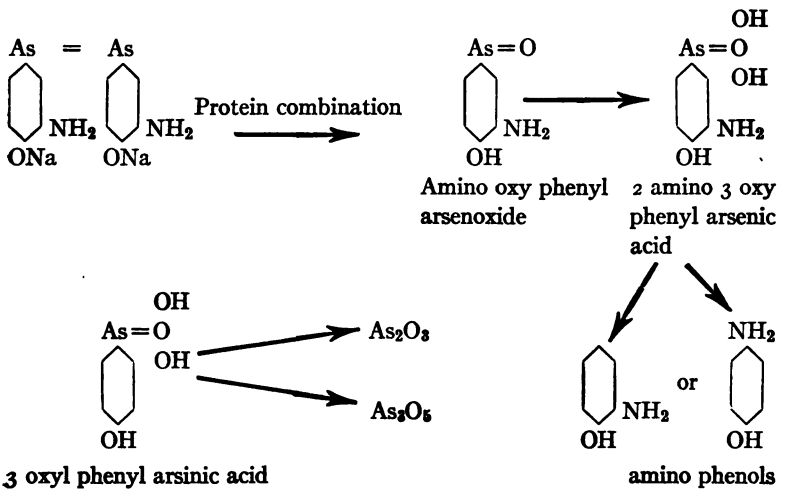
Salvarsan sodium



Neosalvarsan

Trivalent Arsenic more Potent Therapeutically

In the case of trivalent arsenic the effective dose can be introduced with much greater safety and, according to Ehrlich, the more powerful therapeutic action is due to the radical containing the trivalent arsenic, the importance of which was rendered apparent in experiments with trypanosomes and also to the introduction of hydroxy radicals in the para position in the molecules, in which the amido radicals are in the ortho position, relatively to the hydroxy radicals. In the case of these double ring compounds, there is a double arsenic action due to the scission of the salvarsan (or neosalvarsan) molecule between the two arsenic groups giving the action of two trivalent arsenic molecules. The chemical change which takes place in the blood is probably represented by the following formulas: (Ernest Sieburg—*Zeitschr. physiol. chem.*, Vol. 97, p. 53, 1916.)



CHAPTER V

INDICATIONS, CONTRAINDICATIONS AND EFFICIENCY OF ARSPHENAMINE

Particular Indications for Arsphenamine Treatment

It should not be accepted as a fixed rule that all cases of lues are to receive arsphenamine treatment. As elsewhere discussed, there are certain definite contraindications to the use of the arsenical preparations. It is generally accepted, however, that particular indications for the use of arsphenamine can be laid down and it is, therefore, advised that the product be utilized in:

1. All cases of early syphilis possessing distinctive symptoms.
2. In primary cases as an abortive agent.
3. In tertiary and latent cases with a positive Wassermann.
4. In tabes and paresis, congenital syphilis, malignant syphilis, painful periostitis and gummata.
5. In cases in which mercury cannot be used to advantage, when the patients become easily salivated or in which, after long continued mercurial treatment, the Wassermann reaction remains positive.

Contraindications to Arsenical Therapy

Arsphenamine and neoarsphenamine cannot be used indiscriminately upon every luetic person. Therefore a careful physical examination of the patient is an important essential. If any of the following conditions exist these remedial agents should be withheld until the offending obstacle has been removed if such is possible:

Recent cases of myocarditis and valvular disease.

Nephritis, not of syphilitic origin.

Marked diabetes.

Advanced tuberculosis.

Any diseases of the organs of the thoracic and abdominal cavities.

Persons of very advanced years.

Persons possessing an idiosyncrasy against arsenic.

Following acute diseases, especially when depressing sequelæ are present.

Dr. H. H. Morton of Brooklyn suggests that salvarsan be used with extreme caution in brain syphilis, but directs attention to the fact that in acute optic neuritis, choroiditis and interstitial keratitis, it clears up the lesions with great rapidity.

The urine of each patient should be examined before the administration of the drug and cases showing a renal involvement should be denied arsphenamine or it should be given in very small doses.

After each injection of salvarsan and neosalvarsan the urine should also be examined, so that the physician, at all times, may be familiar with the condition of the kidneys.

A trace of albumin and a few casts may be found in the urine the morning after an injection of salvarsan. This should not be considered a contraindication unless considerable albumin is present and the number of casts on the slide are in excess of ten.

The Therapeutic Effects of Arsphenamine

One injection of arsphenamine aids materially in rendering the patient non-infectious to those about him.

The spirocheta pallida disappears from the chancre in from twelve to forty-eight hours after salvarsan injection and the lesion usually heals in from seven to ten days.

Condylomata and mucous patches disappear within a few days after the injection, as do skin and bone gummata.

Dr. H. H. Morton says the "effects of salvarsan in malignant syphilis are brilliant, especially in the cases which are refractory to mercury and iodides."

Mortality in congenital syphilis has been considerably lessened since arsphenamine treatment was instituted.

Salvarsan relieves the "lightning pains" of tabes, although

it cannot restore the nerve tissue which has been destroyed. Tabetic and paretic patients are generally much improved by the use of salvarsan and in some cases the progress of the disease is arrested.

The intraspinous use of arsphenamine in these cases is advocated by some and decried by others, but adherents of both intraspinous and intravenous methods seem to be of the opinion that improvement usually follows the employment of arsphenamine.

Arsphenamine's Therapeutic Efficiency

The efficiency of arsphenamine as a curative agent in the treatment of lues has been so definitely established during the years of its employment that this subject needs only a passing word.

The testimony of a few authorities will demonstrate to the casual reader the place the drug has made for itself in the world of therapy.

Col. E. B. Vedder, U. S. Army (*Syphilis and the Public Health*, p. 259, 1918), says "it has been sufficiently demonstrated that salvarsan is a specific in the treatment of syphilis, and while the fallacy of our original hopes of a 'therapia sterilizans magna' is now apparent, this drug still remains the most potent remedy which we can command. Although it is still possible to treat syphilis by mercury alone or in combination with the iodides in the later stages of the disease, such treatment is distinctly inferior in its results to the proper combination of salvarsan and mercury."

Dr. Loyd Thompson of Hot Springs (*Syphilis*, p. 232, 1918) says "chancres, the syphilodermata, and the syphilomycodermata heal with startling rapidity, the treponemata sometimes disappearing from the lesions within twelve to twenty-four hours, while the symptoms of visceral syphilis and syphilis of the nervous system usually diminish and may disappear altogether following its (salvarsan's) use."

Dr. Cole states in the *Ohio State Medical Journal* that "salvarsan is the most powerful drug now at the physician's com-

mand in the treatment of syphilis and when wisely administered is practically free from all danger or marked unpleasantness." He adds that herein lies the great value of salvarsan (after an injection of salvarsan) that in twenty-four to forty-eight or seventy-two hours the acute, contagious lesions on any patient will be so changed that he will be no longer a direct menace to his friends and society. Cole believes that practically every case of cerebro-spinal syphilis with a high cell count in the spinal fluid will react well and quickly to salvarsan. He has seen "lightning pains" disappear after one or two injections—though this is not always true.

Nine Indications for Salvarsan

Dr. G. F. Lydston of Chicago states in the *Medical Standard* that he is convinced from careful observation that salvarsan is of great value in meeting the following indications:

First. Prompt removal of genital lesions thus lessening: first, the danger of infecting others; second, the danger of detection; third, local discomfort; fourth, the danger of serious complications.

Second. The prevention or prompt removal of disfiguring skin lesions.

Third. Precocious or malignant syphilis.

Fourth. Cases resistant to mercury.

Fifth. Early nerve, brain and visceral lesions, with the exception of renal syphilis in which salvarsan is especially dangerous.

Sixth. Cases of syphilitic cachexia or anemia, which often consist of a combination of overtreatment and syphilis.

Seventh. Syphilis involving the organs of special sense, excepting marked lesions involving the retina. The wisdom of employing salvarsan here is still subjudice.

Eighth. Early tabes and, in some late cases, to relieve severe pain or involvement of the sphincters.

Ninth. Infantile syphilis.

In all cases mercury should be regarded as still our sheet anchor in syphilis.

Arsphenamine as a Prophylactic

It is a matter of common belief that arsphenamine introduced into the system as soon as the initial lesion has manifested itself, or before, in the event the recipient feels he has been inoculated with the spirocheta pallida, will act as a prophylactic.

Indeed the ability of arsphenamine to prevent syphilis from obtaining a foothold in the system has been exemplified in a great number of cases. One of the latest is the report by Dr. A. C. Magian (*Bull. de l'Acad. de Méd.*, Paris, May 20, 1919) to the effect that on March 21, 1918, in the French Hospital at Manchester he inoculated himself in the presence of twenty physicians with some of the serous fluid from a chancre. Less than an hour afterward he was given an injection of arsphenamine, 0.6 gram. None of the classical symptoms, either local or general, which would indicate syphilis, appeared, and although he had a Wassermann taken monthly for a year since that time it has been constantly negative and he has shown no indication whatever of having the spirocheta pallida in his system.

We have known cases in which the physician inadvertently pierced his skin with a needle which had been utilized for the injection of salvarsan. As a matter of precaution, the physician immediately had himself injected with salvarsan and no signs of lues ever developed.

We are of the opinion that salvarsan used in this way will prevent syphilis.

Arsphenamine as a Medicinal Agent in Other than Luetic Conditions

Arsphenamine seems to be of value in conditions other than lues. In the tropics it is used as a more or less routine treatment in filaria, frambesia, malaria, recurrent fever, tick fever and marsh fever, and it has been recommended by some physicians in those conditions in which arsenic is indicated, such as psoriasis, leukoderma, pemphigus, and the like.

Vincent's angina, pyorrhea and "trench mouth" are also among the conditions in which arsphenamine has been employed.

No particular recommendation is made regarding the employment of salvarsan in these diseases, as we have had no experience. We are of the opinion, however, that the use of arsphenamine will be much more general in the future as research evolves ways and means for its use.

The great war has brought about an entire change in treating many conditions. One of the most unique has been described by Dr. A. Brechot, of the French Army (*Paris Medicale*, May 24, 1919). He employed neoarsphenamine intravenously for the purpose of preventing or curing septicemia, and as an adjuvant in furthering and hastening the healing of wounds. He found that in such conditions an intravenous injection of neoarsphenamine, 0.3 gram, was followed by great improvement. According to the cases which he describes, the action of neoarsphenamine became noticeable at least by the third day, and its effect was most beneficial in acute septicemias which were not complicated with marked local lesions.

It was also of benefit in infected wounds in the soft parts which were of recent origin and which had become gangrenous. He did not obtain beneficial results when neoarsphenamine was employed in conditions showing advanced suppuration or where there was an enormous amount of gangrene.

The Comparative Use of Arsphenamine and Neoarsphenamine

Each of these products has its ardent admirers among physicians. Some men insist that one, and others the other is the drug of choice. Personally, we believe that a great many things enter into the matter of a choice between salvarsan and neosalvarsan. Some patients failing to improve with one, make marked improvement under the other, and, believing as we do that every case of syphilis must be individualized and treated according to the particular needs of the affected person, it is impossible to make an unqualified statement as to the value of one as compared with the other.

Drs. Wm. B. Trimble and John J. Rothwell of New York (*J. A. M. A.*, page 1984, 1916) made an interesting study based

on the treatment of 110 patients, and reached the conclusion that neosalvarsan is superior to salvarsan, being much easier of administration, less likely to cause severe reaction, and producing a greater percentage of negative results.

Dr. Oliver S. Ormsby of Chicago (*J. A. M. A.*, page 949, 1917), says that salvarsan and neosalvarsan are the most efficient drugs yet discovered in the treatment of syphilis. As to a choice between the two, Ormsby believes the extensive use of both proclaims their efficiency, so that individual circumstances with the physician and patient must decide which is to be selected. He says the apparent preponderance of opinion that salvarsan is more efficient is offset to a degree by the difficulties of its administration and the more frequent reactions following its use.

Research work and comparative tests will in the not distant future do much toward demonstrating the comparative value of the two drugs.

It is admitted that from the standpoint of the general practitioner neoarsphenamine is the product of choice.

CHAPTER VI

A PLAN FOR ANTILUETIC TREATMENT

Eternal vigilance is the price of freedom from the spirocheta pallida. Immediate, consistent, persistent and proper treatment is necessary to overcome the ravages of syphilis. As soon as a diagnosis of lues is made, it is the duty of the physician to institute treatment. We believe that the great majority of sores on the penis are likely to be chancres and we make it a rule to so regard all sores that put in an appearance ten days or longer after exposure. It is far better to treat a chancroidal case as if it were specific than to "slip up" on a case of chancre. It is well to bear in mind that many sores diagnosed as chancroids reveal both Ducrey's bacillus and the spirocheta pallida and consequently demand antiluetic treatment.

Dark field illumination should be used on all penile sores as soon as seen, and little difficulty is experienced in demonstrating the presence of the spirochete if it is in the field. This is proof positive of the disease.

In certain instances it is possible to abort syphilis by the most vigorous treatment.

Some authorities advise the excision of the chancre as soon as it appears in the belief that, if taken in time, the spirochetes will not be able to penetrate the surrounding tissue, and we believe it is better to be rid of the lesion if it is so situated that its removal will cause no deformity.

Prompt Treatment Demanded

As soon as the diagnosis has been made, it is our custom to give an intravenous injection of 0.3 gram salvarsan or 0.45 gram neosalvarsan, or in the case of a woman 0.2 gram salvarsan or 0.3 neosalvarsan. If well borne by the patient, 0.4 gram salvarsan or 0.6 gram neosalvarsan is given five days later.

Mercury, preferably one-fourth to one-half grain of the bichlorid in the form of a collapsule, is given hypodermically in the buttock two days after the first injection of salvarsan or neosalvarsan and this is repeated three times a week for twelve weeks. If an insoluble mercury is desired we use the salicylate in collapsules of one grain weekly.

Salvarsan or neosalvarsan is then administered at seven-day intervals until six more doses have been used, making the course number eight.

When taken early, these cases show a negative Wassermann and it is our object to keep the reaction negative. One month after the last intramuscular injection of mercury a Wassermann is taken. If negative, another is taken one month later, and, if the result is the same, we wait two months before having another examination made. If still negative we have Wassermanns done bimonthly for two years, by which time, if the reaction continues negative, we feel that a cure has been effected.

If, on the other hand, the first reaction shows positive, we repeat the course of salvarsan and mercury treatment and follow this up until a permanent negative is obtained.

It is not always possible to see our patients at the time the initial lesion presents itself. Many of the cases of lues which appear in the physician's office are beyond the primary stage and abortion of the disease is out of the question.

The Treatment of Longer Standing Cases

It is necessary, in these, to institute intensive treatment, for it is on this rock that we must erect our therapeutic structure. Many a case has gone down before the gales of disease because the house of therapy was built upon the sands of infrequent and inconsistent treatment.

As with the attempt to abort syphilis, we start the patient out with 0.3 gram salvarsan or 0.45 gram neosalvarsan (if a woman, the dose is respectively 0.2 gram salvarsan or 0.3 gram neosalvarsan). Two days later we inject hypodermically in the buttock a collapsule of ¼ or ½ grain mercuric bichlorid. Three

days later comes 0.4 gram salvarsan or 0.6 gram neosalvarsan. If all is well, salvarsan or neosalvarsan is continued at weekly intervals until eight injections have been given and mercury is given three times weekly at intervals for twelve weeks, unless the insoluble form is employed, in which case the injections are administered weekly. The kidneys must be watched for possible irritation. The action of the salvarsan kills most of the spirochetæ pallidæ, while the mercury destroys the spirillæ which are to be found in organs beyond the reach of the arsenic.

Four weeks after the last injection of mercury, a Wassermann is taken. If positive, the salvarsan-mercury course is repeated and is so continued until a negative is obtained.

If negative, the same routine obtains as in the abortive plan.

When a case is taken early, one course of treatment is likely to result in a negative reaction, and the earlier we start intensive treatment the more likely are we to get negatives.

Iodides Demanded in Tertiary and Latent Cases

In tertiary and latent cases several courses of treatment may be necessary to reach the goal. Potassium iodid must not be forgotten in these cases, particularly if gummata or periosteal lesions or other manifestations of late syphilis are present. If the disease has affected the nervous system it is especially indicated. To be effective potassium iodid must be pushed in heavy doses. The drug should also be used in tertiary syphilis with a persistently positive reaction, without involvement of the central nervous system. Indeed there are cases, which, though apparently clinically cured, are serologically not cured, that is, they seem to be permanently positive. Such cases are termed "Wassermann fast" and in the light of our present knowledge it seems impossible to change these positive cases to negative.

If a patient shows a negative and later develops a positive, we have proof that he still has a focus of infection in his body and must be given another course of treatment.

The provocative injection plays its part as related in the chapter entitled "Provocative Wassermann Reaction."

We believe good treatment calls for the use of this procedure in early cases. If negative reactions result, we feel that we have reason to pronounce a cure. If spirochetæ are still in the system, we should know it, and the provocative injection is the only agent, except time, which will make their presence known.

In tertiary and latent cases a Wassermann of the spinal fluid must be made and **the reaction of both blood and spinal fluid must be repeatedly negative** before the case can be pronounced cured.

Salvarsan and Mercury Necessary

Dr. C. L. Barewald of Davenport, Iowa, in a paper read before the Scott County Medical Society, March 4, 1919, states that after using the various preparations on the market he found that salvarsan is by far the best, as it gives better results and more efficient elimination. He has given more than two thousand intravenous injections of salvarsan without experiencing any bad results. He emphasizes the fact that syphilis is not cured by salvarsan alone and that mercury must be included in the treatment. He gives salvarsan once a week for eight weeks and at the same time uses mercury, preferably by inunction.

Intensive Salvarsan Treatment

Dr. S. Politzer, of New York (*Jour. Cut. Dis.*, Sept., 1916) is an advocate of the most intensive type of salvarsan treatment in acute cases. As soon as a positive diagnosis is made, he gives three injections of salvarsan in large doses at intervals of twenty-four hours, and follows this by a course of eight weekly injections of salicylate of mercury. If the treatment is begun after the appearance of the rash, this course of salvarsan and mercury treatment is repeated after a pause of two months and again after a similar interval. After three courses within the first year, he suspends treatment if the Wassermann reaction is negative.

If the treatment is begun a year or more after infection, treatment should be continued until negative, and two more additional courses of treatment given, even though the reaction may be negative.

Dr. J. L. Murray of Toledo (*Ohio State Med. Jour.*) is an advocate of a similar method. His plan is to give a small dose of salvarsan on three successive days, followed by eight weekly injections of salicylate of mercury.

In the secondary stage, Murray gives these intensive courses at intervals of three or four months regardless of the Wassermann reaction.

CHAPTER VII

THE TECHNIC OF ARSPHENAMINE ADMINISTRATION

The Intravenous Administration of Arsphenamine

The fundamental principle of drug administration is based upon the proper usage of the remedial agents which are to be employed. Carelessness in technic or lack of necessary information regarding a drug has often seriously injured good preparations.

Three prime requisites stand out as necessary to the satisfactory administration of a drug: (1) knowledge of the drug and its properties; (2) a perfect understanding of the patient and his idiosyncrasies; (3) confidence and due precaution on the part of the administrator.

In the injection of any drug by the intravenous method rigid asepsis is a most important factor.

During the past two years over two million doses of arsphenamine have been administered with varying degrees of success. After a careful study of the situation in hospital and private practice, we have evolved a method of administration, which provides safety and precaution in the highest degree for the physician and the patient.

Preparation of the Drug

The apparatus necessary for the administration of salvarsan includes:

An adjustable bracket or stand, and a table for this stand to rest upon.

Two glass cylinders of 250 c. c. capacity; one for holding the solution of salvarsan and the other, distilled water.

THE INTRAVENOUS INJECTION OF ARSPHENAMINE

The apparatus necessary, including all the articles mentioned on pages 42–43.

Rubber tubing leading from each cylinder to a Morton three-way stopcock, on the end of which the needle is attached.

Fordyce or other needles of fine, medium and large calibre, the size to be determined by the vein.

2 c. c. syringe and hypodermic needle for epinephrin.

An abundant supply of freshly prepared double distilled and sterilized water, or 0.4 per cent sodium chlorid solution.

A tourniquet of rubber tubing or a rubber catheter.

A glass cylinder (250 c. c.) in which to mix the solution.

Sterile gauze and sterile cotton.

A glass funnel for filtering the solution.

Tincture of iodin or alcohol.

A bottle of freshly prepared C. P. sodium hydroxid—15 per cent or normal sodium hydroxid—4 per cent.

A bottle of collodion for sealing the point of the puncture after administration.

Lastly, the drug itself.

Apparatus.—The mixing cylinder should be thoroughly washed with distilled water and drained for a few minutes, the stopper tied loosely to the neck of the cylinder and then the stopper and neck covered with a piece of gauze. The combination should be sterilized by dry heat and when cool, the stoppers inserted without removing the gauze. The gauze is tied around the upper part of the stopper so that it can be used as a protection to the stopper during its subsequent use in mixing.

There is no objection to the method of boiling the cylinder for twenty minutes in the sterilizer except that it requires additional sterile distilled water for rinsing before use. All of the other apparatus should be sterilized just before using and extreme care should be exercised to avoid using the apparatus while it is still hot. The reason for this care is to avoid the decomposition of the salvarsan solution before it is used.

It is a well-known chemical fact that **too hot water is one of the chief factors in causing decomposition and subsequent reactions.** Just before using the apparatus, it should be rinsed out with sterile distilled water.

Distilled Water

The water problem in the making of salvarsan solutions is a question of real importance to physicians, especially to those who have occasion to administer arsphenamine at infrequent intervals. It is at all times necessary to employ **freshly distilled** water and not that which may be several days or weeks old. It is absolutely unsafe to send to a neighboring town for distilled water or the 15 per cent sodium hydroxid, and by so doing the physician takes a considerable risk.

It is a well-known fact that water contains many inorganic salts as well as much nitrogenous matter. To remove these impurities, the process of distillation is used but, through neglect, some of the water may be allowed to boil over into the side tube and thereby vitiate the efforts of purification. Water also contains volatile material of a gaseous nature and it is important to remove these impurities. Time and space do not permit a detailed discussion of a method which will yield what is known as "chemically pure" water or "conductivity water." However, a general method is presented for securing relatively large quantities of water suitable for intravenous use.

Any suitable type of metal distilling apparatus provided with a block tin condenser will answer the purpose. A manufacturer of chemical apparatus can easily provide this type. In using it, care should be used in preventing the possibility of mechanical overflow. This provides a roughly distilled water contaminated with volatile gases. This grade of distilled water should be used for obtaining sterile, freshly glass-distilled water. There are several ways of carrying out this procedure.

The simplest technic is to place the water in any glass-distilling apparatus and add calcium oxid or alkaline permanganate to absorb carbon dioxid and destroy organic matter. The contents should be heated to boiling and the distillate collected in a flask suitable for later sterilization if the water is not to be used as soon as cool. A continuous distillation can be carried on by this method.

DISTILLING APPARATUS

A simple type for physicians who have no gas, electricity or running water, or who lack any one of these three conveniences. Description of this apparatus is found on page 45.

A Simple Distilling Apparatus

In case only a relatively small quantity is to be utilized, omitting the permanganate, it is well to distill off at least one fourth and discard it and to collect the remainder for use. For the benefit of those who are limited in their facilities the apparatus shown in the accompanying picture is presented.

This type of apparatus is designed for those who lack gas, electricity and running water or any one of the three conveniences. It consists of an ordinary aspirating bottle which may be used as a source of water supply by putting ice into water and allowing the ice water to flow through the condenser as a means of cooling the water vapors. The rest of the apparatus consists of a pyrex distilling flask suitably connected to a glass condenser with a flask for collecting the water. The whole apparatus is held in place by a single iron stand with the necessary clamps and rings. The apparatus is cheap and very compact as well as usable. In fact it may be used by any physician who has need for distilled water and has gas and running water available. If the water is used within a half hour, it is sterile and suitable, otherwise it is necessary to boil the water before using and then cool it to room temperature (68–77° F.) before using it. **Under no circumstances should hot water be used** with salvarsan or neosalvarsan.

The Drug

In manufacturing arsphenamine every care is used in protecting the drug from undue exposure to oxidation and moisture and it is reasonably safe to say that the product is very uniform in composition and therapeutic properties. Every ampule is carefully examined for any imperfection by the flotation method before it leaves the laboratory. During transportation accidents may happen to the glass container and in every instance the ampule should be **placed in 95% alcohol for 20 minutes,** to detect any imperfections such as a minute crack, which is invisible to the naked eye, and at the same time to sterilize the

ampule. After examination the ampule is dried with a piece of sterile cotton or gauze.

It is imperative that neither the contents of ampules that may have been damaged in transport, nor the remainder of previously opened ampules should be used, as this involves serious danger to the patient. While the ampule is in immersion, all the instruments and utensils which are being utilized in the administration should be boiled in distilled water.

The Solution

Before discussing this most important phase of the technic in arsphenamine administration, it may not be amiss to make reference to the fundamental principle of therapeutics. All therapeutic action is based upon the laws of chemical affinity which are in turn governed by the laws of chemical dynamics and equilibrium. The demands on the drug are such that it is essential the number of reactions should be reduced to a minimum. To meet these requirements it is necessary to follow certain definite laws of chemistry.

Some physicians insist on using the drug in concentrated solutions and pay little attention to alkalinization. **Alkalinization and concentration are the two most important factors in preparing the solution for injection.** It is a well-known fact that if solid sodium hydroxid is dropped into concentrated hydrochloric acid considerable heat is evolved, due to chemical action in forming the compound sodium chlorid. The same applies to arsphenamine when it is injected into the blood stream. A new compound is formed, one in which the proteins of the blood stream and the protozoa combine with the arsenical. The rapidity and amount of combination are the factors which determine whether there will be disturbances in the host.

The cause of this chemical reaction is to be found in the fundamental laws of energy changes. All of the energy changes are easily subdivided into intensity factors, and capacity factors. The intensity factor of any form of energy or change tends toward equalization of differences which condition develops when the

DISTILLING APPARATUS

A simple and inexpensive water still for physicians who have laboratories in connection with their offices.

rate of injection is very slow and the dilution is great. When two substances are brought together, the tendency to equalize the difference in concentration and tolerance is adjusted by the body. This can only be accomplished when the organism has an opportunity to meet these new conditions and establish an equilibrium where the drug changes into a soluble compound in the body, making due allowance for decomposition of the arsphenamine and the rate of elimination.

To all those familiar with dynamics it will at once be observed that the "ideal" solution is the one which gives the most uniform results chemically, physically, and therapeutically. The concentrated solutions should yield abnormal results unless the time factor is so carefully controlled that an ideal condition is obtained.

Upon this scientific basis it is now suitable to prepare the solution.

Preparation of the Solution

A dilution of 100 mg. (0.1) to 25 c. c. of water is probably within the safe limits. The United States Army and the United States Public Health Service have recommended **a dilution of 100 mg. in 30 c. c. of water.** This is a most conservative recommendation in view of the fact that there may be other abnormalities existing in the patients. It is also much better to err on the side of precaution and conservatism. The size of the dose recommended is generally conceded to be a 0.4 gram dose which should be given more frequently. This subject will be discussed at length in another chapter.

The ampule of salvarsan should be opened by filing it in two or three places near the point where the body of the ampule joins the tip. A smart blow on the end of the ampule will break it off cleanly.

About 50 c. c. of room temperature (68–77° F.) sterile, freshly distilled water should be poured in the mixing cylinder and the contents of 0.4 gram ampule lightly scattered on the surface of the liquid, using care in maintaining asepsis. The stopper should be placed in the flask and gentle agitation follow. The powder

will dissolve readily in the cold water and when every particle is in solution alkali should be added at once, according to the table below.

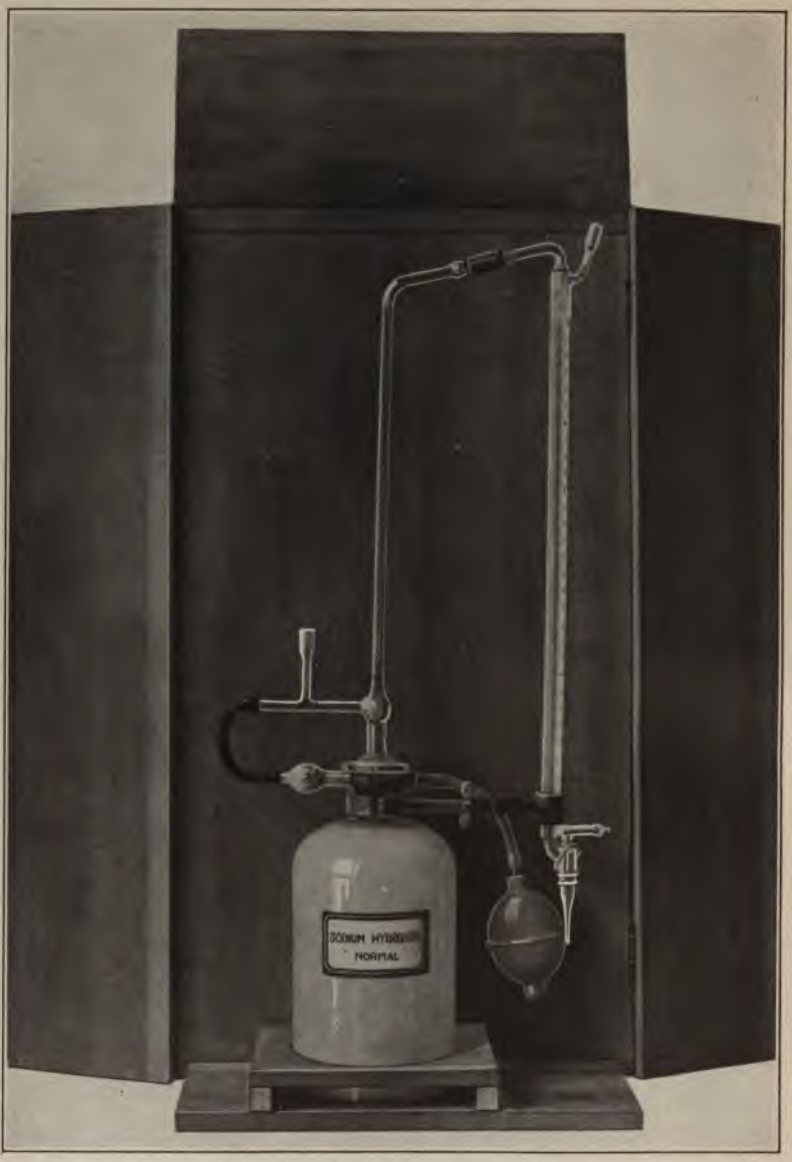
An ampule of 0.4 gram requires 3.36 c. c. normal sodium hydroxide (4 per cent) or 16 drops of 15 per cent sodium hydroxide. It is imperative that the alkali be free from carbonates and gelatinous material. For this reason it is best to use freshly prepared alkali unless other proper precautions can be taken. Again the stopper should be inserted in the mixing cylinder, which should be inverted a couple of times, and then the volume increased to 100 or 120 c. c. After a gentle shaking, if the proper care has been exercised, the solution will be ready for intravenous administration.

The salvarsan solution should be used immediately. In warm weather additional care should be used to avoid unusual temperatures.

Table of Normal and 15 Per Cent Sodium Hydroxid Necessary

Weight of drug	c. c. of normal NaOH required for disodium salt	Drops (aver. = .07 c. c.) 15% NaOH required for disodium salt
.1	0.84	4
.2	1.68	8
.3	2.52	12
.4	3.36	16
.5	4.20	20
.6	5.04	24
.7	5.88	28
.8	6.72	32
.9	7.56	36
1.0	8.40	40

The mechanism of the change taking place during the alkalinization is shown by the following table which indicates the most satisfactory form in which the drug should be given.



Apparatus for Holding Normal Sodium Hydroxid Solution

The solution can be kept in the bottle indefinitely and, as it is measured out by a burette, absolute accuracy is certain, and perfect alkalinization is effected.

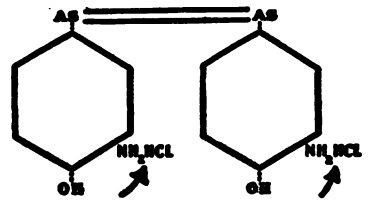
The box holding the apparatus is shown with the sides and top turned back and the front cover removed.

CHEMICAL TRANSFORMATION OF SALVARSAN

INTO THE DISODIUM SALT

Required for Intravenous Injection

I SALVARSAN



Salvarsan as it appears on market

I

SALVARSAN DI-HYDROCHLORIDE.

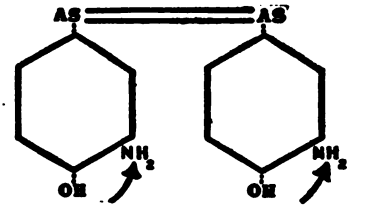
Yellow Powder about 31.50% Arsenic.

Soluble in cold water.

Acid to litmus.

Solution not suitable for intravenous administration.

II SALVARSAN BASE



Sodium Chlorid Na Cl is formed at this stage of alkalinization

II

SALVARSAN BASE.

Precipitated upon addition of 12 drops of 15% sodium hydroxide solution or

2.52 cc. of normal sodium hydroxide solution per 0.6 gram Salvarsan.

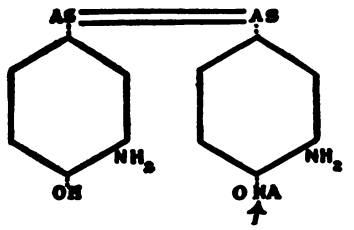
Insoluble yellow precipitate.

Causes reactions.

Not suitable for intravenous administration.

III MONO-SODIUM SALT

OF SALVARSAN



III

MONO-SODIUM SALT OF SALVARSAN

Formed upon addition of 18 drops of 15% sodium hydroxide solution or

3.78 cc. normal sodium hydroxide solution.

Just soluble in water.

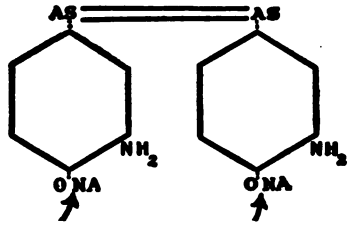
Clear yellow solution.

Slightly alkaline to litmus.

Not suitable for intravenous administration.

IV DI-SODIUM SALT

OF SALVARSAN



IV

DI-SODIUM SALT OF SALVARSAN

Formed upon addition of 24 drops of 15% sodium hydroxide solution or

5.04 cc. normal sodium hydroxide solution.

Completely soluble in water.

Clear yellow solution.

Ready for intravenous administration in dilution of 0.1 gram in 30 cc. of freshly distilled water.

This is the only form in which Salvarsan solution should be used.

MEDICAL LIBRARY

Necessity for Proper Alkalinization

Some physicians have a tendency to discontinue the alkalinization at the point where the precipitate disappears and the solution becomes clear. **This is a dangerous procedure** for the reason that the tendency to form precipitates is greatly increased at this alkalinity, since the presence of carbonates, carbon dioxide, magnesium and calcium salts combine more readily in this condition than in the form of the disodium salt (Myers, *U. S. Public Health Reports*).

Under these conditions the precipitates not only cause mechanical stoppage in the capillaries, but also extract calcium and magnesium from the blood. These last two elements are necessary for cardiac stimulation and when they are removed the blood pressure obviously falls below normal. Such a condition aids in allowing the precipitates to collect and block the capillaries. Calcium forms an insoluble salt with arsphenamine and this can only be prevented by the use of a more strongly alkalinized solution, namely, the disodium salt. These facts hold true with all the preparations on the market at the present time. Arsphenamine is a substance which tends to aid blood coagulation and therefore there is an eminently good reason for the proper administration of the drug.

D. E. Jackson and M. I. Smith of the Hygienic Laboratory, United States Public Health Service have shown that there is no perceptible fall in blood pressure when the drug is injected as it should be. When it is introduced rapidly and in concentrated solution, the pressure falls very slowly and collapse may result. These facts tend to stimulate the manufacturer to keep up the high standard of purity of the product.

In the early history of the American manufacture of arsphenamine, some products of poor quality appeared on the market but with the present high standards in force, salvarsan par excellence is being produced, having the advantages of being easily soluble in cold water, of having a uniformly high arsenic content, as well as possessing the same therapeutic power of any arsenical produced at any time.

The Filtering of the Salvarsan Solution into the cylinder which is to be utilized for it is urgently recommended. A small bit of glass may have chipped off the ampule during the filing and found its way into the solution and extraneous matter may get into the preparation despite the greatest care. We advocate the use of heavy layers of thoroughly sterilized gauze for purposes of filtering, rather than to employ absorbent cotton. It was formerly possible to get a sterilized cotton which was satisfactory for purposes of filtration, but a well-known genito-urinary surgeon recently traced some reactions following salvarsan administration to the use of absorbent cotton.

Upon chemical analysis he discovered the presence of an acid which undoubtedly caused the reaction. Calcium-chloro-hypochlorite (CaCl O Cl), incorrectly called chloride of lime, and known by the trade name of bleaching salt of lime, is used in bleaching cotton. The chlorite present in the cotton was due to the chlorine contained as natural chlorites and probably to chloride of lime remaining in the cotton due to incomplete neutralization and washing in the process of preparation of the absorbent cotton. The acid present was undoubtedly due to the formation of either a little hydrochloric acid from the bleaching salt of lime by the action of sulphuric acid, by which the cotton is treated to neutralize the alkalinity of the bleaching lime, or to the presence of both hydrochloric and sulphuric acids.

Physicians using absorbent cotton who get reactions would do well to make a chemical analysis of their cotton.

After filtering the solution of salvarsan into one cylinder we next run 100 or more c. c. of freshly distilled sterilized water into the other cylinder, the rubber tubing having been previously attached to each cylinder. The tubing should then be raised up and down a sufficient length of time until all the bubbles of air have disappeared. The tubing can be squeezed in various places so as to make certain no air is present. The needle should be attached by short rubber tubing to the Morton three-way stopcock, with a window made of glass tubing between the stopcock and the needle, so that when the puncture is made the

operator can ascertain his whereabouts in the vein by the back flow of blood.

Preparation of the Patient

After having determined that there are no contraindications to the administration of arsphenamine or neoarsphenamine, the preparation of the patient for treatment should begin the night before the administration, when an active catharsis must be induced. **At the time of the injection, the gastrointestinal tract must be entirely clear.** If the treatment is to be given in the morning, the patient should eat no breakfast and, if in the afternoon, no luncheon. We make it a rule to allow **no food in the stomach for at least six hours** before the injection, thus insuring a clean intestinal tract. There is no objection to a cup of weak tea at meal time, but no solid food of any type should be permitted.

It is necessary to **examine the urine before each injection.**

When these details have been carried out and the patient is ready for the administration of the drug, he should be laid in a recumbent position on a surgical table or, if the injection is given at home, on a bed. If the surgical table is used, it is very easy to affix an arm thereto, upon which the patient's arm can rest. This gives the operator the advantage of having the field of operation perfectly steady at all times.

The Choice of the Vein

The vein of choice is the cephalic just below the junction with the vena mediana cubiti, as at this place a level spot is offered, whereas a little higher up the bend of the elbow is encountered with its attendant inconvenience for the entrance of the needle. If for any reason this vein is not available, the basilic, just above or below the junction with the median antibrachial, offers the most attractive site of entrance.

Sometimes the accessory cephalic is large enough for the easy insertion of a needle and as a dernier ressort the physician is sometimes compelled to use the median antibrachial near the wrist or one of the oblique branches connecting the basilic and cephalic.

THE INTRAVENOUS INJECTION OF ARSPHENAMINE

The patient, by twisting his shirt sleeve with the left hand, makes a very satisfactory tourniquet. His right hand firmly grasps a salvarsan container for the purpose of "bringing out" the vein.

The veins near the wrist are usually so small that much skill is required for the introduction of a needle of fine calibre.

When the vein has been chosen, the arm is thoroughly cleansed with alcohol or iodin well over and around the point of the intended puncture. The area should be covered with sterile gauze until the actual injection is made.

The patient's arm should rest on sterilized towels and it will be much easier to put a sterile gauze pad just below the spot where the injection will be made, so that the blood can be caught. It is needless to observe that the operator and his assistant must "wash up" as for any operation.

The tourniquet is then applied to the patient's arm two or three inches above the bend of the elbow joint, and an oval body such as the wooden box in which salvarsan comes is placed in his hand to assist in bringing out the vein. He is told to clench the fist as if to strike a blow and within a few seconds after the application of the tourniquet (which can be either a rubber catheter or a piece of ordinary rubber tubing) the vein should stand out sufficiently large to enable the operator to proceed.

There is a difference of opinion as to making the injection with a needle attached to the tubing or without it, and this is a matter which an operator must decide for himself. When the needle is attached he can observe the back flow through the window. When it is unattached, there is no difficulty in ascertaining the presence of the needle in the vein by the backward flow. We prefer the latter method.

Introduction of Needle into Vein

Fixing the chosen vein between the thumb and finger of one hand, with the needle between the thumb and index finger of the other hand, the point of the needle should be inserted into the vein as near the middle thereof as possible. When entrance has been effected, the needle should be slowly moved from side to side to make certain that the wall of the vein has not been pierced. If the vein is very large, it is better to enter at an angle, so there may be no tearing of the lumen.

As soon as the physician satisfies himself that he has placed

the needle squarely in the vein, the tourniquet should be released and the rubber tubing attached. The stopcock is then opened to permit the entrance of about 25 c. c. of distilled water into the vein.

The Introduction of Distilled Water before the Arsphenamine

The purpose of the introduction of the distilled water first is that if there should be any leaking around the point of entrance caused by the tearing of the vein the use of distilled water will obviate any pain, or possible inflammation caused by infiltration. The arsphenamine solution, if allowed to leak out, would cause a burning sensation and considerable difficulty might result from an infiltration. After the injection of 25 c. c. of distilled water the stopcock is turned and **the salvarsan introduced very slowly,** the operator allowing **at least two minutes for each decigram** of salvarsan. When the full amount has been injected, he should switch back to the distilled water and thus wash out the vein.

After the needle has been removed it is better for the patient to hold his hand perpendicularly for a short time, pressing a pledget of sterile gauze over the point of entrance. When the bleeding has entirely stopped a drop of collodion should be placed over the point. There is no necessity to bandage the arm.

The patient should be kept in a recumbent position for from fifteen minutes to an hour and he should remain quiet the remainder of the day. We have given in our office many injections of salvarsan to patients who have gone long distances—some as far as one hundred miles—within an hour after the injection. This practice is not recommended, however, and is only advisable in times of emergency. As reactions may follow several hours after the injection it is always well to have the patient near at hand.

Helpful Hints in Treatment

There are many small points in connection with the injection of arsphenamine which, if carried out, are helpful. One of the first is the use of sharp needles. We suggest a very sharp, short-

THE INTRAVENOUS INJECTION OF ARSPHENAMINE

The introduction of the Fordyce needle into the vein. It will be observed that the tourniquet is still in place.

beveled needle instead of one with a long sharp point, as the long-pointed type may catch in the wall of the vein and cause a leak. A dull needle is not only likely to tear the vein and cause subsequent infiltration, but the pain attendant upon its use is discouraging to the patient. The use of such a needle is particularly difficult when the patient happens to be of a neurotic type.

If the veins do not stand out perfectly with the application of the tourniquet, a few smart slaps on the arm over the intended point of entrance will often have the desired effect. Another method of enlarging the vein is to have the patient, with his arm very rigid, bend his wrist forward so that the clenched first will be at an angle of 45° to the forearm.

Some small veins can be brought out by the application of sterile gauze wrung out in hot water.

Walking up three or four flights of stairs or bending over and touching the floor with the fingers, without flexing the knees, are also recommended for bringing out the veins.

In injecting a vein, if for any reason the blood does not flow freely and the operator desires to use the same vein higher up it is well to leave the first needle in place and make the injection through another needle, as by the removal of the first needle a hematoma may result.

We desire to **warn particularly against using the stylet of the needle** to cleanse a needle which may seem to be clogged up. An embolism is likely to follow such prodecure.

Too rapid injection of salvarsan may bring about a feeling of dyspnea and oppression, due to the over-dilution of the blood in the right heart, with the result that the blood going into the lungs contains an insufficient amount of oxygen.

At times it is not possible to have an assistant when administering salvarsan and the removal of the tourniquet may prove somewhat awkward to the operator. The patient, if a man, can very easily be taught to grasp his undershirt or, if he wears the sleeveless type, the outside shirt in one finger and roll it up so tightly that the circulation will be completely impeded. This makes a most efficient tourniquet and can be released upon a word from the physician.

The Use of Vasodilators

Dr. George E. Barnes of Herkimer, N. Y. (*Boston Medical & Surgical Journal*, May 15, 1919), offers an ingenious method for facilitating the insertion of the needle into small veins by the use of vasodilators. He recommends nitroglycerin as the particular product to be used. Barnes believes that, while this acts acutely, there is also good reason to use other remedies for a continual state of normal tension of the vessels and suggests such products as gelsemium, cannabis, pulsatilla, conium, lupulin, cramp bark and cactus. He suggests that the nitroglycerin be taken in the proper dosage in tablet form, chewed up, dissolved in the saliva and swallowed. Such a drug, however, should not be used until it is ascertained whether or not the patient is likely to have a reaction.

A Window over the Vein

Dr. E. G. Ballenger, of Atlanta (*Genito-Urinary Diseases and Syphilis*, p. 477, 1913) has a unique method of inserting a needle into a vein which is not easily palpable or visible. By means of a small round stiletto he had fashioned for the purpose, a window is made in the skin over the vein, the skin first being pulled to one side, so that the stiletto will not injure the vein. This leaves a window twice the size of the needle directly over the vein. With the vein well distended and often visible through the hole, it is easy to slip the needle through the opening directly into the vessel.

Concentrated Injections of Arsphenamine

Some men of great eminence are utilizing salvarsan in the concentrated method. Dr. E. L. Keyes, Jr., in his splendid book on *Urology* observes, page 827, that "the original technic calls for the administration of 300 c. c. of fluid. At present the usual allowance is 10 c. c. of distilled water for every decigram of the drug to be injected. The dose for the adult male is three or four decigrams; for the adult woman, three decigrams; for the infant, one centigram. . . .

THE INTRAVENOUS INJECTION OF ARSPHENAMINE

The needle having been introduced into the vein, the assistant removes the tourniquet so that the physician can switch on the sterile distilled water preparatory to the introduction of the arsphenamine.

"The injection is made either by gravity or with a 30 c. c. piston syringe or by a syringe to which is attached a three-way stopcock and one rubber tube leading into the bottle containing the salvarsan, while the other leads to the needle in the patient's arm. Whatever the method employed, it is essential that the salvarsan be given slowly and that at least five and preferably ten minutes be taken for the injection of the 30 c. c. Therefore, **the gravity method is the safest.**"

The concentrated method of salvarsan introduction is doubtless a safe one in the hands of so experienced and skillful an operator as Dr. Keyes, but for the average medical man, part of whose time must necessarily be given to other lines of medicine, we feel that the concentrated method is unsafe. Dr. Keyes' technic is presented to show that the concentration of the fluid is not regarded as dangerous by one of our most eminent colleagues, but the earnest suggestion is made that men who have not had as much experience in the administration of salvarsan as Dr. Keyes do not emulate his example.

Dr. Theodore H. Smith, of Detroit (*Jour. Mich. State Med. Soc.*, April, 1917) believes that concentrated solutions of salvarsan are more effective than dilute ones in that the salvarsan in the concentrated solution is more slowly excreted, but he admits that the one objection to this method is the urgent necessity of a perfect technic in the intravenous injection itself. He says that if the needle does not lie accurately within the vein, a small amount of the concentrated solution entering the perivascular tissue will produce results even more dangerous than with the more dilute solution.

Injection of Salvarsan into the Superior Longitudinal Sinus

One of the largest venous channels in the body is the longitudinal sinus lying at the posterior angle of the anterior fontanel. Through this medium salvarsan can be injected. It has been used for a number of years for the injection of saline solutions and for blood transfusion.

Dr. Louis Fischer of New York, read a paper on "The Value of the Longitudinal Sinus in Transfusion and for Rapid Medica-

tion" before the Section on Diseases of Children of the American Medical Association in June, 1918. He expressed himself as thoroughly convinced that the difficulty of entering a vein the size of the median basilic or even the femoral, in infancy, makes the longitudinal sinus the route of choice for the introduction of any medication into the system of an infant or for transfusion.

Dr. Fischer has perfected a technic which physicians can well follow. He wraps the infant in a mummy bandage, well pinned, so that the arms and legs are confined, and places the child flat on its back. The head is steadied on both sides by an assistant while the needle is inserted into the sinus. He finds that he can enter through the anterior fontanel until the child has reached the end of its second year. As the sinus grows wider toward the back of the head, Fischer recommends the point of entrance to be as far posterior as possible.

The needle is pushed through the posterior angle of the fontanel and directed downward and backward in a line with the sagittal suture. The sinus is very superficial and there is no need of entering deeper than 1 or 2 mm. For this purpose a sharp-pointed needle ½ inch long of 20 or 22 gauge is best adapted. When the needle penetrates the sinus, resistance is lessened and the same sensation is observed as when a needle enters the dura mater in performing a lumbar puncture.

In giving salvarsan by this method, Dr. Fischer advises that it be administered by gravity slowly. A cylinder from 30 to 100 c. c. capacity can be used. One end of a piece of rubber tubing is attached to the cylinder and the other end has a connecting tip which fits into the needle. A stopcock should be at the end of the cylinder or near the end of the tubing. The needle is inserted into a small syringe attached. By a slight aspiration the physician can determine whether the sinus has been entered; if so, the syringe is detached and the apparatus, which has been filled and the air expelled, is connected.

The child should be watched carefully and its color, pulse and respiration noted.

Dr. Fischer is of the opinion that there is no danger of losing too much blood by the puncture, even though a large needle is used.

Dr. Vincent of Boston warns against injecting too rapidly lest increase of intra-cranial pressure cause vomiting and disturbed respiration. These difficulties are soon overcome when the flow of blood has been temporarily checked. Air pressure in the tube must be released by detaching the syringe before the needle is withdrawn.

Blood Precipitates

Danysz and Fleig have written extensively about the formation of precipitates when salvarsan is introduced into the blood by the intravenous route. **The cause of many reactions has been traced to the use of acid and under-alkalinized solutions.**

Herring (*Münch Med. Woch.*, Vol. 57, No. 50, 1911) has shown that in rabbits the acid solution is twenty times as toxic and in dogs ten times as toxic as a properly alkalinized solution. When an acid solution is introduced into the blood stream a yellow, insoluble precipitate is formed and this prevents the flow of the blood through the capillaries. In this condition calcium and magnesium are precipitated as insoluble salts of salvarsan. The removal of these elements from the blood stream has a tendency to reduce the blood pressure and in the presence of the insoluble blood precipitate, it is practically impossible for the blood to circulate through the capillaries.

If a properly alkalinized solution (disodium salt) is used, no fall in blood pressure is observed and, in addition, the formation of precipitates is almost entirely eliminated. If the monosodium salt is used, the carbonates, sulphates and alkaline phosphates cause a precipitation of the drug very easily on account of the hydrogen ion concentration, resulting from the chemical combinations. An alkaline solution (many hydroxyl ions) tends to eliminate these conditions. The isolation and chemical analysis of these blood precipitates will be found in a recent U. S. Public Health report.

The Intramuscular Administration of Arsphenamine

The intramuscular method of injection was in the early days of salvarsan hailed as an easy and convenient manner of introducing

the drug into the system. The pain attendant upon the injection proved to be a *raison d'être* for discarding the method in favor of intravenous medication on the part of the great majority of salvarsan users. The intramusular method is still employed in such cases as present no suitable veins, and again by physicians who believe the results from the intramuscular method excel those from intravenous introduction.

Col. Charles F. Craig, U. S. Army (*The Wassermann Test*, p. 180, 1918) has demonstrated the truth of this assertion by a study of 500 cases, of which 209 were treated by the intramuscular injection of the alkaline solution, 249 by the intravenous injection of the drug, and 42 by combined intramuscular and intravenous injections.

This table illustrates the effect of the method of administration upon the Wassermann reaction:

Method of Administration	*Total Cases*	*Became Negative*		*Remained Positive*	
		Number	%	*Number*	%
Intramuscular....	209	159	76.0	50	24
Intravenous.....	249	101	44.5	148	55.5
Combined.....	42	28	66.6	14	33.3
Totals.....	500	288	57.6	212	42.4

It will be observed, from a study of the table, that the effect of intramuscular injections of salvarsan upon the reaction is much more pronounced than other methods of administration. This method of administration has been almost abandoned by the profession, and in the army it has been entirely replaced by the intravenous method, owing to the pain and complications that follow the injections and the time lost in hospital. However, there is no question in Craig's opinion that the intramuscular method is infinitely more efficient in treatment than the intravenous, as shown by the results upon the Wassermann test, for of the 209 cases so treated, most of them receiving but one injection of 0.6 gram salvarsan, 159, or 76 per cent became nega-

tive, and fewer cases treated by the intramuscular method relapsed than when treated intravenously.

The figures given for the intravenous method are below what they should be for the reason that the majority of the cases studied only received one intravenous injection. Further observations upon this method of administration and its effect upon the Wassermann reaction have shown that with from three to five intravenous injections the results are as good as those obtained with the intramuscular injections, but the data here given are sufficient to show that the Wassermann reaction can be rendered negative by only one intravenous injection in at least 40 per cent of the cases.

Intramuscular Method Superior to the Combined

The effect upon the reaction of the combined intransmuscular and intravenous method of using salvarsan was determined in 42 cases, of which 66 per cent became negative, thus indicating that the results were not as good with the combined method as with the intramuscular method alone. However, this result was due to the fact that a number of the intramuscular cases had two or even three injections of salvarsan, and it is considered that one intramuscular injection of the drug is equal to at least three intravenous injections so far as the effect upon the Wassermann test is concerned.

As should be expected, the effect of treatment with salvarsan upon the reaction increases with the number of doses of the drug that are administered, regardless of the method of administration. Of 200 cases receiving one intramuscular injection of salvarsan of 0.6 gm., 152, or 76 per cent became negative, while of 9 cases receiving two intramuscular injections, 7, or 77.7 per cent became negative. There is little difference between these two groups of cases so far as the apparent effect upon the Wassermann test is concerned, but the number of cases receiving two intramuscular injections is too small to allow of our basing upon them any accurate statistics, as a large number of cases would undoubtedly give a higher percentage in this class of cases.

Of the cases treated by the intravenous method, 177 were

given one intravenous injection of 0.6 gm. of salvarsan, and 72, or 40.6 per cent became negative; 52 were given two intravenous injections of the same dose, of which 22, or 42.3 per cent became negative; while 10 cases were given three intravenous injections, of which 7, or 70 per cent became negative. There was but little difference in the percentage of negative results obtained in those given one and two intravenous injections; and it will be noted that two intravenous injections did not have as much effect upon the Wassermann reaction, as one intramuscular injection. The percentage of negative results obtained with three intravenous injections, however, approaches closely to that obtained with one intramuscular injection, and justifies the assertion, based upon this obvious experience, that one intramuscular injection is equal, in its effect upon the Wassermann reaction, to three intravenous injections of a salvarsan.

Preparation of Arsphenamine for Intramuscular Use

Several methods of preparing salvarsan for intramuscular injection are in vogue.

Ehrlich set forth the following method for the preparation of alkaline solutions for both intramuscular and intravenous injection:

Ehrlich's Method

"Into a narrow-necked, glass-stoppered, sterile, graduated glass cylinder of 300 c. c. capacity, 30 to 40 c. c. sterile *freshly distilled water of not more than room temperature are measured.* The salvarsan, for example 0.5 gram, is sprinkled on the surface of the water and dissolved by vigorous agitation. To the solution, after it has become absolutely clear and no undissolved particles can be seen, 19 drops of 15% sodium hydroxid solution are added by means of a pipette, drop by drop. This causes a precipitate which dissolves on shaking. The clear yellow solution is now filled up to 250 c. c. with sterile 0.5% saline solution prepared from chemically pure sodium chlorid and sterile FRESHLY distilled water.

" Salvarsan solutions must always be freshly prepared. In the

preparation of the alkaline solution it is imperative to observe that the salvarsan must be completely dissolved in distilled water (*not saline solution*), at ordinary temperature and that the solution does not show any gelatinous particles whatever before the sodium hydroxid solution is added. The sodium hydroxid solution is *not* added gradually, but at once. The precipitate produced thereby must be completely dissolved prior to the further dilution of the alkaline concentrated salvarsan solution with 0.5% saline solution. The sodium chlorid must be chemically pure. Tap or spring water is unsuitable. **Hot water must NOT be used in preparing the solution of salvarsan.** Should the solution not be quite clear or become slightly turbid after a few minutes, a few more drops of sodium hydroxid solution should be added, a drop at a time and waiting 2 or 3 minutes after each drop to see if this quantity suffices to clear the solution. Each 50 c. c. of this solution contains 0.1 gram salvarsan.

"If no graduated glass cylinder is at hand, the concentrated salvarsan solution may be prepared in a small glass-stoppered flask, and after the addition of sodium hydroxid solution and complete clarification, poured into the saline solution. The solution should be filtered if necessary.

"**Intramuscular Injections** may be made with the alkaline solution as above described, but in this case only about 5 c. c. of fluid are required. For its preparation one proceeds by well triturating in a sterile mortar, for instance 0.5 gram salvarsan with 19 drops of 15% sodium hydroxid solution and then diluting with distilled water to the desired volume. The injection is made into the upper exterior sections of the gluteal muscles. The injection should be made deeply but very slowly, so as not to cause hemorrhage. The neighborhood of the sciatic nerve must be carefully avoided. Intramuscular injections may also be made with simple triturations of salvarsan in fatty oils 1:10 (Oleum Amygdal. dulc., Oleum Sesami, Oleum Olivæ).

"In all cases the area of the injection must be previously disinfected with iodin-benzene or tincture of iodin. After intramuscular application the injected fluid should be distributed by massage.

"In sensitive persons the site of injection may be completely anesthetized by a previous injection of 2 c. c. of a 1% novocain solution. Hydropathic measures, as moist compresses, hip-baths, etc., or the application of warm compresses, may be successfully employed to prevent afterpain. The internal administration of pyramidon has proved very efficacious."

The Alt Method

The Alt alkaline solution method is: "Ten c. c. of sterile distilled water are placed in a beaker of about 50 c. c. capacity, the salvarsan added and triturated with a glass rod until completely dissolved. Normal (4 per cent.) sodium hydroxid solution is now added in the proportion of 0.5 c. c. to each 0.1 gram of the drug. The stirring is continued until a precipitate is formed and is partially redissolved. The alkali solution is now added drop by drop until the opacity nearly clears. It is not desirable to permit the solution to become completely clear, as such a solution is more irritating to the tissues than the slightly tubid solution. The total volume is now made up to 20 c. c."

The Michaelis Method

The neutral suspension of Michaelis is prepared as follows: "The salvarsan is dissolved in a solution prepared by adding 0.3 to 0.6 gram of sodium hydrochlorate to 16 c. c. of very hot sterile distilled water in a wide-mouthed graduated cylinder. From 3 to 5 c. c. of normal sodium hydroxid solution are added and the mixture thoroughly stirred. Three drops of a 0.5 per cent. solution of phenolphthalein in 70 per cent. alcohol are added as an indicator, which causes a red color to develop. Then 1 per cent acetic acid solution is added, drop by drop, until the red color disappears. The salvarsan is precipitated as fine yellow floculi and finally a few drops of the normal sodium hydroxid solution are added to recolor slightly the phenolphthalein. The solution is then ready for injection."

Oily Emulsions

Oily emulsions are also employed intramuscularly to advantage. The firm of Hynson, Westcott & Dunning, of Baltimore,

puts out ampules of salvarsan in oil ready for injection, which have met with favor at the hands of advocates of intramuscular medication.

British Army Method

Lt. Colonel L. W. Harrison, R. A. M. C., in charge of the Military Hospital, Rochester Row, England, reports favorably (*Brit. M. J.*, May 5, 1917) on the use of the intramuscular method of neosalvarsan administration. He used neosalvarsan dissolved in 10–15 minims of distilled water and injected into the gluteus medius muscle. This gave a fair amount of pain with some lameness after, but when accompanied by a hypodermic injection of morphin it proved as comfortable as any other method. He also utilized the same amount in deep subcutaneous injection, made under the fascia covering the gluteus medius muscle. This was less painful immediately afterward, but often caused the formation of a tender lump on the site of the injection some days later.

Another method was the intramuscular and deep cutaneous injections of neosalvarsan emulsified in creo. camph., melting point, 20° C. There was some pain for a few hours afterward but as a rule the patient would allow the site of the injection to be massaged vigorously the following days.

The most useful method was the injection of six decigrams neosalvarsan dissolved in 1 c. c. of a 4 per cent. solution of stovain and made up to 2 c. c. with creo. camph., melting point, 15° C., or with camph. phenique. This was the most comfortable injection to use. It was made about a point three finger breadths below the crest of the ilium on a line joining the tuber ischii with the point on the crest of the ilium, which is perpendicularly above the great trochanter, when the patient is upright.

As a result of these injections, Harrison feels that the intramuscular or subcutaneous method is superior in immediate therapeutic effect to the intravenous, that the spirochetes disappear from syphilitic lesions just as rapidly after the first intramuscular as after the first intravenous injection, and that the Wassermann reaction is more quickly influenced.

An American Method

Still another method which has been successfully utilized by some American physicians is to mix 1 oz. each of a 2 per cent novocain solution and chemically pure glycerin. To 4 c. c. of this combined mixture are added the contents of an ampule of neosalvarsan. They are thoroughly mixed together, antiseptically of course, and 1 c. c. is injected through each of four needles —two in each buttock. By the utilization of the four needles, there is not so much foreign substance in the given parts of the muscle and there seems to be less likelihood of trouble. The novocain anesthetizes the part for some time and takes away the initial sting of the injection.

After Treatment

In England and on the Continent it is the habit, after giving an intramuscular injection, to cover the surrounding parts with sterilized absorbent cotton fixed with elastic collodion. The patients were instructed to rest in bed for twenty-four hours and, according to various reports, the majority of them complained only of stiffness in the hip and thigh and occasionally of pain in the lower extremity.

Some physicians also utilize a clay dressing, like antiphlogistine, in place of cotton. It is their custom to cover the entire gluteal surface with a thick layer of properly heated antiphlogistine and to cover this with gauze, and over that absorbent cotton. This application seems to work well following the intramuscular injection and, not only aids in the prevention of pain and to a considerable extent prevents any abscess formation, but enables the patient to attend to his ordinary affairs.

Intramuscular Methods not Popular

Notwithstanding the experience of Col. Harrison, as above recounted, the vast majority of practitioners seem to prefer the intravenous procedure of administering salvarsan and neosalvarsan. Their reasons are based upon the fact that the local disturbances, accompanied by pain and possible abscess, when

the intramuscular method is employed, seem like a needless punishment of the patient. Moreover, the patients themselves demur and express a preference for any treatment which will eliminate the suffering so commonly accompanying the intramuscular introduction of arsenical products.

Administration of Arsphenamine by the Rectum

More or less has appeared in the medical press concerning the introduction of salvarsan into the system by way of the large intestine. Various means have been advocated for the introduction of salvarsan in this manner. This method is not advocated by medical writers except in children and adults whose veins are exceedingly difficult of entrance. We have employed it with success in different individuals, whose veins have not been utilizable.

The patient has the usual pre-salvarsan preparation, so far as the gastrointestinal tract, etc., is concerned. In addition the lower bowel must be thoroughly cleansed by an enema. The patient is then placed on the table in the Sims or genupectoral position and a sterilized catheter is inserted into the rectum a distance of six inches.

Our technic has been to slowly and carefully emulsify salvarsan in 1 ounce of olive oil by thoroughly stirring the powder into the oil with a glass rod. When this has been properly accomplished the oily emulsion is drawn up into a sterilized glass syringe and is forced through the catheter into the rectum. Another ounce of olive oil is then introduced in a similar way through the same catheter. The catheter is withdrawn and the patient is allowed to remain upon the table for one hour. If the injection is given at the home it is better to keep the patient in bed for several hours so as to prevent any escape of the salvarsan emulsion.

It will be observed that arsphenamine employed in this manner is not alkalinized by sodium hydroxid but is put directly into the olive oil.

Some physicians employ salvarsan for rectal injection by making an aqueous solution, but we prefer the oil on account of its blandness and because there is less opportunity of irritating the

mucous membrane of the intestine. This method has been followed in giving weekly injections to patients and we have had no complaint of bowel irritability.

When aqueous solutions are used sodium hydroxid is employed exactly as in making up a solution for intravenous injection. The amount of distilled water should be about 30 cubic centimeters.

Patients remaining in the genupectoral position any length of time complain of great weariness, so that after ten minutes we permit the patient to assume the Sims position.

The physician must exercise care not to permit any escape of the injected contents.

We have seen no occasion to utilize opium or any of its derivatives in this form. Some operators have added a little laudanum for its soothing effect, but our experience has not made this necessary.

CHAPTER VIII

THE TECHNIC OF NEOARSPHENAMINE ADMINISTRATION

There are two methods of introducing neoarsphenamine into the system; one, the dilute, and the other, the concentrated. The preparation of the patient for either method is the same as that for arsphenamine, and every detail as set forth in the preceding pages, as to the physical condition of the patient, the gastro-intestinal toilet, and the urinary examination, should be carried out in its entirety.

The choice of veins is the same.

Dilute Intravenous Administration of Neoarsphenamine

The apparatus necessary for the dilute administration of neosalvarsan is practically identical with that for salvarsan, with the exception that the use of sodium hydroxid is prohibited.

The ampule of neosalvarsan should be immersed in 95 per cent alcohol for twenty minutes and all the instruments and utensils should be boiled in distilled water. When these latter are sufficiently cool, the amount of freshly distilled and sterilized water which is to be utilized for the injection should be run into the solution cylinder. The quantity of water differs with the amount of neosalvarsan to be utilized. This table will set forth the proper amounts:

For Dosage		I (0.15)	use	25 c. c.
"	"	II (0.3)	"	50 c. c.
"	"	III (0.45)	"	75 c. c.
"	"	IV (0.6)	"	100 c. c.
"	"	V (0.75)	"	125 c. c.
"	"	VI (0.9)	"	150 c. c.

This water must be **room temperature and never hot,** as hot water is likely to produce oxidation and give rise to reactions.

The method of opening the neosalvarsan ampule is identical with that of salvarsan. The contents of the ampule should be scattered lightly over the surface of the water and the product will then very promptly go into solution. It is very seldom one finds occasion to agitate this solution, even in the slightest degree.

The neosalvarsan solution is then filtered into the cylinder which is to be utilized for that purpose, and the freshly distilled and sterilized water as it is used in the administration of salvarsan should be placed in the other cylinder.

The technic for removal of the air and for preparing for the injection is identical with that already given for salvarsan, and practically every point brought out in the chapter on salvarsan can be duplicated in this connection.

The Concentrated Intravenous Administration of Neoarsphenamine

One of the reasons for the widespread popularity of neoarsphenamine is the ability of the physician to administer it in concentrated solution. The amount of fluid to be used seems to be a matter of opinion. Some employ only 10 c. c. of water in giving 0.9 gram neosalvarsan and others employ solutions up to 50 c. c. The favorite quantity of solution is about 25 c. c.

Two reasons are advanced for the use of the concentrated solution. The first, and doubtless the most general, is that it is "the lazy man's method." Some believe that as the necessary preparation for the injection is reduced to a minimum, such a small amount can be hurriedly injected.

The second reason is that some physicians hesitate to introduce a large and what they deem an unnecessary quantity of fluid into the circulation.

In the first instance it is doubtless true that there are practitioners who employ neosalvarsan on account of its ease of preparation. For some reason they feel that the addition of sodium hydroxid to the salvarsan solution requires a degree of skill or patience which they do not care to exercise. Again, some men are inclined to the newer product on account of the small

amount of apparatus required for the injection. With others, time seems to be the deciding factor. They begrudge the few extra minutes demanded by the use of the gravity apparatus and consequently seek the quicker and more convenient way of utilizing the services of a Luer syringe.

Reasoning of this nature is entirely wrong. The matter of time should not enter into the practice of medicine, especially when so grave a disease as lues is the enemy to be combatted. "The best is none too good" for the patient, and only the best method of giving a remedial agent should be considered.

The relative value of salvarsan and neosalvarsan is considered elsewhere and is not germane to the subject now under discussion, but we do most emphatically protest against the use of neosalvarsan or any other drug merely because it is easy of application.

Time an Important Factor for Safety

If upon due reflection and study of existing conditions the physician determines upon the use of neosalvarsan, he should bear in mind the strictures placed upon the rapid injection of the drug by Dr. George W. McCoy, U. S. P. H. S., and discussed at length in another chapter. He believes and rightfully, we feel, that **two minutes should be given to the injection of each decigram** of arsphenamine or twelve minutes to each maximum dose of 0.6 gram. As one and one-half decigrams of neoarsphenamine are equivalent to one decigram of arsphenamine, the natural assumption is that Dr. McCoy believes twelve minutes should be consumed in the injection of 0.9 gram neoarsphenamine.

If his sensible and necessary injunctions are carried out the time factor will not enter into the consideration of the use of concentrated solutions of neosalvarsan.

Of the ease of preparation, owing to a lessened amount of apparatus, nothing need be said, for the fact remains that the method offers great convenience in this particular connection and we are heartily in sympathy with those who employ it on that account.

The second reason, *i. e.*, the amount of water put into the circulation, opens up a question concerning which there has been much discussion. Each school has arguments which appear to offer conclusive proof that it is correct in its deductions. We must admit with real frankness that long usage of both methods has not convinced us that either is wrong.

We formerly employed 300 c. c. in administering 0.6 gram salvarsan. No untoward effects were observed from the use of so much fluid. Later, the amount was reduced to 250 c. c. and finally to 180, or 30 c. c. per decigram, and we have no present expectation of going below this amount in the administration of arsphenamine solutions.

It must be admitted that in a few unguarded moments, salvarsan has been injected by us for experimental purposes, in a concentration as low as 7 c. c. per decigram. Grave fears followed the use of this low concentration, and the patients were carefully observed for unpleasant symptoms, which, however, happily did not ensue.

One swallow does not make a summer, but the experience has not been repeated lest some of the reactions we read about might fall to our lot.

In the use of neosalvarsan we formerly used the gravity method, giving every decigram of neosalvarsan in 20 c. c. or 180 c. c. for a full dose. Added experience caused the amount to be lessened from time to time. When the use of a dilute solution of neosalvarsan is believed to be preferable, from 100 to 130 c. c. is deemed the proper amount. If it is felt the patient can or should have a smaller amount of water, a concentration ranging from 20 to 50 c. c. is given. Full blooded persons are generally picked for the greater concentration. As a rule, all things being equal, 25 c. c. is the average amount of fluid utilized.

Danger of too Concentrated a Solution

At the instigation of a colleague, who enthusiastically related marvelous serological results following 0.9 gram neosalvarsan in 10 c. c. of water, this method was employed for several injections

THE INTRAVENOUS INJECTION OF NEOARSPHENAMINE

The apparatus necessary, including the articles mentioned on page 73. The already prepared neoarsphenamine solution will be observed in the wide-mouthed beaker in the centre of the picture.

on four patients, all men in good general condition. After the injections each man complained that "the medicine is awfully strong," or "that shot had too much kick" or otherwise expressed his disapprobation of the method, not knowing of the undue concentration. They experienced dizziness and in some instances nausea, and one man felt an unpleasant tingling of the fingers. As these men had received three or more injections in concentrations of 25 c. c. or greater, it was deemed advisable to abandon the use of the more concentrated solutions. It is worthy of note that the subsequent use of the usual concentration elicited no complaint from these patients, nor did they exhibit further dizziness, nausea, or other symptoms, during the remainder of their course of treatment.

It is hardly necessary to give an abundance of evidence as to the value of the concentrated method, on account of its wide usage. It may not be amiss, however, to quote the experience of Favre and Massia (*Press medicale*) who successfully gave 3,150 injections in an average of 18 c. c. of water each. They employed a very fine needle, were able to enter small veins, and found that this high concentration showed no evidences of vein irritation. Reactions were few and very mild in character. They believe that the use of mercury with neosalvarsan lessens the probability of reactions.

We urgently advise the use of mercury with salvarsan and neosalvarsan in all cases where tolerated, not so much for its anti-anaphylactic as for its anti-luetic action.

Technic of Concentrated Method

In the utilization of this method, the patient is prepared as for the dilute injection of either salvarsan or neosalvarsan and, instead of using the apparatus for the dilute injection, a Luer syringe of from 25 to 50 c. c. capacity takes the place of the double glass cylinders, with the bracket, rubber tubing and three-way stopcock. The solution is made in a wide-mouthed glass graduate instead of in a tall, glass cylinder.

After the ampule has been sufficiently immersed in alcohol, it is opened and the contents sprinkled on the surface of the

freshly distilled water in the graduate. The amount of water depends on the ideas of the physician. Our practice is as a rule to give it in about 25 c. c. The neosalvarsan very speedily goes into solution. As the solution should be filtered, another glass graduate can be utilized for this purpose. As soon as this has been completed, the solution is drawn into the sterilized Luer syringe. The needle is then introduced. When the operator is certain that the needle is squarely within the vein, as indicated by the backward spurting of the blood, the syringe is attached to the needle and the contents very slowly injected. The same length of time should be consumed in administering the concentrated solution as in the dilute. This means that the operator must push the piston of his syringe so slowly as to be almost imperceptible.

The amount of time which Dr. McCoy recommends—twelve minutes for the full dose—shows that in giving a 25 c.c. concentration not over 2 c.c. should be injected a minute.

Subcutaneous Injection of Neoarsphenamine

Neoarsphenamine can be injected subcutaneously without difficulty provided the operator has a very careful technic. The great desideratum is not to put it into the fatty tissues, into the fascia or into the muscles.

One of the firmest advocates of the subcutaneous administration of neosalvarsan is Dr. Joseph A. Thomas of Valdosta, Ga. He has used this method for six years, has given a very large number of injections in this manner and regards it very highly indeed. The preparation of the patient is looked upon as a very sacred trust by Dr. Thomas. He pays especial attention to the gastro-intestinal tract and insists that the diet on the day of administration be exceedingly simple and he particularly emphasizes that no tomatoes should be ingested, as he has had cases of vomiting where this article of food has been taken, but he has never seen vomiting from any other cause.

He is also particular about testing the secretions of the mouth. If he finds an acid condition he utilizes alkalis until the system

THE INTRAVENOUS INJECTION OF NEOARSPHENAMINE

Tourniquet has been removed and the concentrated solution is being introduced into the vein VERY SLOWLY through a Luer syringe. The gauze under the needle absorbs the blood which flows back through the shank of the needle when it is first introduced into the vein.

becomes practically free from acidity. He believes this to be essential for the prevention of unpleasant after-effects, although in a letter to the author he says that he has not yet had any reactions.

Dr. Thomas then examines the patient carefully for indications as to renal, cardiac or neurological disturbances. Those caused by syphilis do not form contraindications to the drug but, if present from other causes, he treats the cause before going further with neosalvarsan administration.

Dr. Thomas' Technic

For the employment of neosalvarsan subcutaneously, Dr. Thomas utilizes (1) a 10 c. c. Luer syringe with a 20 gauge platinum needle; (2) a syringe with a small needle for the local anesthetic; (3) a glass graduate which will hold 20 c. c.; and (4) freshly distilled, sterilized water.

After the ampule of neosalvarsan has been thoroughly sterilized by immersion in alcohol, he opens it and dissolves the contents of the ampule in 10 c. c. of freshly distilled water at room temperature.

The patient is placed upon his abdomen and the skin at the angle of the scapula is painted with iodin around the point an inch or two in circumference. It is then anesthetized with a few drops of cocain. The neosalvarsan solution is drawn up into the Luer syringe and is injected **UNDER the skin** and not in it or in the fascia but in the connective tissue between the skin and the fascia. Dr. Thomas lays particular stress upon the importance of this point.

The injection should be given very slowly. He advises that the operator make certain the needle is free and not in the skin by gently moving the needle from side to side. Upon the completion of the injection the site should be massaged thoroughly, so that there may be a wide-spread distribution of the solution under the skin. This massage prevents the formation of a lump. The point of entrance of the needle is covered with sterile gauze and adhesive.

Dr. Thomas says that very little pain follows this method of administration and when it is observed the pain will practically always be found to be intercostal and largely referred to the anterior aspect of the chest. The patients feel as if they had a pain over the heart, but the pain in Dr. Thomas' opinion, is of small consequence and it has been very seldom necessary for him to administer an opiate.

The advantage of the subcutaneous administration of neosalvarsan over other methods is that it is unusually simple, is without danger, gives at least as good results as the others, and there is practically no after-pain and no detention from business. Dr. Thomas believes that the action of the drug is prolonged for about two weeks. He has injected several hundred patients in this manner and has never had any serious after-effects and only one of his patients has been compelled to go to bed. In this instance the temperature went to 105° F. This patient was in his secondaries with a malignant infection and the medical attendant feels that the cause of the rise in temperature was due to the liberation of many endotoxins following the administration of the spirochetecide.

THE INTRAVENOUS INJECTION OF NEOARSPHENAMINE

The injection having been satisfactorily completed, the assistant covers the point of entrance of the needle with sterile gauze, exercising some pressure. When the bleeding stops the site is covered with collodion.

CHAPTER IX

THE METHODS OF EMPLOYING THE MERCURIALS AND IODIDES

The Intramuscular Method of Injecting Mercury

The intramuscular injection of the soluble or insoluble forms of mercury requires considerable care and should not be regarded lightly.

The favorite site for injection is about one inch from the crease of each buttock and the parts must be sterilized, preferably with tincture of iodin.

Platinum needles of 20 gauge are best adapted for this work, especially when soluble preparations are being used. The needles should be two inches long, so that the mercury can be deposited in the muscle and not in the fat or subcutaneous tissue. Careful examination of the needle should be made before each injection to ascertain any structural weakness. If a **needle is broken off** in the gluteal region the parts must immediately be laid wide open and the part extracted, for needles in that section of the body are rapid travelers.

The needle must be thoroughly sterilized before use and after the injection the bore must be cleared of the detritus, lest some may be left in the bore and, having partially decomposed, be injected into the body at the time it is next employed.

When any form of mercury is to be injected, we strongly recommend an all glass, 2 c. c. Luer syringe.

In carrying out the operation of injection, after the site has been sterilized, we plunge the needle, minus the syringe, deeply into the muscle, with one short stab. This method causes the patient much less pain than slow penetration.

If blood comes out of the shank of the needle, it should immediately be withdrawn, as a vessel has been entered. We have seen patients collapse after an injection of mercury when the

syringe was attached to the needle and no precaution against the entrance of a blood vessel observed.

If blood does not follow the introduction of the needle, the syringe should be attached and the contents of the barrel slowly injected.

We heartily condemn undue haste in making these injections as we believe much of the soreness following this form of medication is due to too rapid introduction.

After the mercury has been deposited in the muscle, the needle is withdrawn and the part slowly and thoroughly massaged under a piece of gauze. This acts to prevent the lumps which appear following gluteal injections, forming the so-called "cobble-stone" buttocks.

As soon as bleeding stops, the point of entrance is sealed with collodion to prevent possible infection.

The Inunction Method

Many physicians believe the inunction method is the best, especially if the rubbing can be done by a person experienced in such work. This method has the advantages of causing no pain, of promptly and thoroughly saturating the body with the drug, and of non-interference with the digestive tract. Inunction is quite necessary in persons who are old or debilitated, or very fat, and in pregnant women, as these types cannot stand injections.

The inunction has an added advantage in that it is stored up in the follicles of the skin and is eliminated through the urine long after the rubbings have been discontinued.

The old-fashioned unguentum hydrargyrum is often used, but we prefer an ointment made as herein set forth, as it leaves no trace on the skin and is not unpleasant in odor:

100 parts of mercury are mixed with 15 parts of anhydrous lanolin and 3 parts of olive oil. Carefully stir, adding the mercury in small quantities, but only when no more mercury pellets are visible. Then add a nearly cold mixture of 112 parts of lard and 70 parts of mutton tallow, this latter mixture having been prepared by melting together, and mix the whole carefully. The

resultant salve is of bluish-gray color and no mercury pellets should be visible to the naked eye.

Anatomical Sites for Inunctions

We suggest, if possible, inunctions just before retiring on seven successive days on these anatomical locations:

1st day—Right and left calves.
2nd " Right thigh.
3rd " Left thigh.
4th " Abdomen.
5th " Chest.
6th " Right arm and forearm.
7th " Left arm and forearm.

The rubbing should be continued for twenty minutes or until all the mercury has disappeared.

After the inunction on the seventh day, the patient should take a hot, soapy bath and the following day commence another seven day series.

The patient should wear woolen undergarments and change them only after the seventh day bath.

The inunctions are continued as long as the case demands and each case must be individualized.

Administration by the Mouth

We mention this method only to condemn it and believe the physicians who pursue this line of treatment are following an ignis fatuus.

Many a case of tabes and paresis has followed the use of mercury *per os*, the patients meantime being sublimely unconscious of their ultimate fate.

Continued use of mercury by this means impairs the power of the alimentary tract to absorb it and anemia, diarrhea and general debility often follow its continued use.

Fumigation and Inhalation

These methods are recommended when there are extensive ulcerating lesions, involving the deeper structures but are not

suggested for ordinary cases. When indicated, however, these means are of real value.

Intravenous Method

This is not yet sufficiently perfected to permit of discussion of a helpful nature. We doubt not that eventually the intravenous route will form one of the standard methods.

Form of Mercury to be Used

The question arises as to whether one will use a soluble or insoluble form of mercury. The insoluble in the form of the salicylate is very popular, although, both calomel and gray oil have their ardent advocates. For example, Dr. J. A. Fordyce, if he employs an insoluble form, utilizes gray oil "in the form of mercurial cream, of which 5 minims represent 1 grain, in a series of ten or twelve injections, or salicylate of mercury 40 per cent suspension in doses of 1 to 3 grains, gradually increased, ten to twelve injections constituting a course."

We have utilized this form of treatment with results not entirely satisfactory. Our dissatisfaction was largely due to the soreness which was likely to follow the injections and particularly to the formation of lumps in the buttocks, the "cobble-stone" buttocks, in which condition mercury was found to be unabsorbed, sometimes weeks after the original injection.

We thereupon experimented with the succinimid, which is a soluble product. This was found to work well in clinics where the patients were men used to very heavy work and who were not easily affected or disturbed by localized soreness, but in private practice it proved to be altogether too painful, nor did the benzoate work to our satisfaction.

The soluble mercury of choice we have found to be the bichlorid, which we ordinarily administer in the beginning of treatment in $\frac{1}{4}$ grain doses. If that is readily taken, the dose is increased to $\frac{1}{2}$ grain and then to 1 grain.

Dr. Fordyce (*Amer. Jour. Med. Sci.*, October, 1916) advised giving a soluble mercury intramuscularly every other day and quoted the bichlorid as his preference of the soluble forms,

SYRINGE AND NEEDLE FOR INTRAMUSCULAR MERCURIAL INJECTION

The needle should be 2 inches long, constructed of platinum or steel.

The syringe is of the ordinary 2 c.c. glass type.

giving from twenty to thirty injections either daily or every other day.

A Convenient Means of Mercurial Administration

One objection to the hypodermic use of mercury has heretofore been the frequent inability to obtain an absolutely certain dosage of mercury, especially where it has been put up in an oily suspension by the local pharmacist. Several years ago there came to our attention an ingenious method of holding insoluble or soluble mercurials in the form of collapsule hypo-fills, which consist of bulbs made of gelatin holding an exact amount of the mercurials. By means of these collapsules we carried on a long series of experiments utilizing the salicylate, calomel, succinimid, benzoate and bichlorid. The mercurial is held in a base containing neutral vegetable anhydrous fats and when introduced into the body breaks down in the form of alkaline palmitates and glycerin. The bichlorid is readily absorbed, the injection is followed by practically no pain and the "cobblestone" buttock is something unknown.

The great advantage of the use of collapsules is that the physician is certain of exact dosage and he is also given a most convenient method of administration. Our experience has been that the use of mercury in this form seems to increase the body weight and the arsphenamine is very materially aided.

From the cut given herewith it will be observed that the gelatin top of the collapsule is clipped off, and the contents squeezed into a 2 c. c. Luer syringe, which is warm from the previous sterilization, and it is, therefore, melted sufficiently to permit of immediate injection into the body.

Advantages and Disadvantages of Soluble Mercury

The great advantage of mercury in the treatment of syphilis is to have it as constantly in the system as possible.

It might seem almost suicidal to advocate the use of bicholorid of mercury in from ¼ to 1 grain doses. This, however, is the dosage which Fordyce has employed in his clinics for a long time without any difficulty, and we have also utilized it to the very

best advantage. It means, however, that the patient should come every other day for treatment and, while this can be accomplished so far as the ordinary dispensary patient is concerned, it is often difficult for the private patient unless he be in a hospital.

Another disadvantage of bichlorid is the possibility of a renal nephritis. We have never seen such a condition but the possibility is ever present and must be most carefully considered.

The use of bichlorid means that **the urine must be constantly examined** so that the condition of the kidneys can be at all times known to the physician.

If the patient can come to the office every other day, or even twice a week, we **recommend the bichlorid**; if it is impossible and the patient can only be seen once a week, **the salicylate is preferable.** In some cases one grain of bichlorid injected once a week has been absorbed so slowly that we have been content to give weekly injections of one grain each.

Iodides

The employment of the iodides in the treatment of syphilis has undergone a very radical change since the introduction of salvarsan as an anti-luetic agent. It was formerly a part of the stock treatment of the syphilitic and after vigorous mercurial medication he was placed upon the iodides, preferably the iodid of potassium. Despite the fact that this drug disarranges the stomach of many patients, it was very generally utilized, although at times other preparations of iodin, such as salts of sodium, strontium, and ammonium, have been used. There are on the market a number of proprietary products containing iodides, which have been formulated in combinations, tending to eliminate the uncomfortable and unpleasant features caused by taking the raw iodides.

Spirochetæ not Affected by Iodin

We have learned, however, that iodin has little or no effect upon the spirochetæ. This was first brought to the attention of the profession by Colonel (then Captain) H. J. Nichols, U. S. Army (*Journal of Experimental Medicine*, p. 196, 1911).

THE INTRAMUSCULAR INJECTION OF MERCURY

Contents of a collapsule of bichloride of mercury being squeezed into a 2 c.c. glass syringe.

On the table is the necessary apparatus for use in intramuscular injection.

THE INTRAMUSCULAR INJECTION OF MERCURY

Clipping off the top of a collapsule of bichloride of mercury to permit the introduction of the contents into a 2 c.c. glass syringe. On the table are the collapsules, syringe, 2 inch, 20 gauge platinum needle, sterile gauze and cotton, and collodion.

Clinical observation has demonstrated that the drug does not change the Wassermann reaction and it has practically no effect upon primary syphilitic lesions. The facts would seem to condemn iodin as a drug for use in syphilis; however, it has a very definite place in the treatment of tertiary syphilis as well as in syphilis of the nervous system. The particular effect of the drug seems to show itself upon the gummata. Just how it works to produce this effect upon gummata is a discussed question, but the fact remains that in the conditions mentioned it is of value.

Iodid of potassium can be used by the mouth or by hypodermic injection and some syphilologists have utilized it by intravenous injection and also by enema. The most common method of oral administration is that of the saturated solution; 100 grains of the potassium iodid are dissolved in sufficient water to make 100 drops. Each drop, therefore, contains 1 grain. It is usual to start the patient off with 10 drops one hour after each meal in a half glass of milk or water and to increase one drop at each dose or three drops a day until the patient shows signs of intolerance. By giving the drug an hour after each meal the potassium iodid finds a more ready reception in the stomach, because the starchy contents have been changed into sugar.

Another method of administration is the formula of Ricord. He did more to popularize the drug in the treatment of syphilis than any other man. This formula is:

Kali iodidi 4.0
Syrupi corticis aurantii 250.0
M. Sig. One tablespoonful three times a day.

If the drug is to be administered hypodermatically, from 4 to 8 grains are given in 50 c. c. solution and any pain which may accompany the injection can be corrected by the introduction of codein to the solution.

We cannot speak of the intravenous use of potassium iodid as we have had no experience therewith.

If the enema form of administration is used, the large bowel should be thoroughly cleansed with an ordinary enema; then it is

well to inject from 1 to 3 drams of potassium iodid in peptonized milk to which have been added 5 drops of laudanum.

Only Heavy Doses of Iodides are Effective

The great value of the iodides is observed in heavy doses. Many physicians are in the habit of prescribing 10 grains three times a day. There is no more advantage of putting this amount of iodid into the patient's stomach than into his shoe. If results are to be obtained, **the drug must be administered in heroic doses.** We have seen many cases in which from 100 to 125 grains were administered three times daily. In these cases, particularly those in which gummata were present, the results were a little short of marvelous, as the lesions would actually seem to fade away under this heavy dosage.

One of the difficulties in taking the drug are the coryzal symptoms which follow the administration of comparatively small amounts. This is due to the fact that the average dose seems to be excreted by means of the nasal mucous membrane. The large dosage is eliminated by the kidneys and causes little or no nasal complications.

Potassium iodid in large doses is something of a heart depressant and it is urged that when patients are given these large amounts they be not permitted to carry on heavy physical work; they should be watched with considerable care.

The amount of potassium iodid which the patient can absorb varies with the individual; some show signs of iodism after a very small amount of the drug. As about 80 per cent. is excreted daily there is an accumulation in the body from the daily dosage. Therefore, a heavy dose should be employed until the patient has reached his limit when the dose should be moderated.

Iodism

Iodism is first brought to the patient's attention by a metallic taste in the mouth or by a coryza, with sneezing and the other symptoms of a head cold. In some instances this coryza becomes somewhat severe, but it passes away by a diminution or a complete cessation of the drug for the time being.

THE INTRAMUSCULAR INJECTION OF MERCURY

After the area has been sterilized with alcohol or iodin, the 2 inch needle is plunged directly into the depths of the gluteal muscles.

The use of potassium iodid is very often attended with gastro-intestinal disturbances as well as dermatological lesions, such as iodid pimples, which are closely analogous to acne vulgaris.

The physician should do everything in his power to prevent over-stepping the bounds of tolerance in the administration of this drug. It is well to have daily examinations of the urine made to observe the excretion of iodin. Dr. Loyd Thompson (*Syphilis*, p. 251, 1916) recommends mixing 2 c. c. each of urine and pure hydrochloric acid and adding a few drops of chloroform. The presence of iodin is indicated by a pink coloration of the chloroform upon settling to the bottom of the tube, following its inversion two or three times. In the event that iodin is not discovered, the physician would do well to watch the case slowly lest iodism appear.

Resumé of the Treatment of Syphilis

Examination of Patient.—Patient to be examined very carefully to see if any contraindications to arsenical treatment be present.

Urine to be examined before the injection.

No food in the stomach for six hours before injection or four hours thereafter, and patient to rest in bed after the injection.

Dosage of Arsphenamine or Neoarsphenamine

Drug dissolved in **room-temperature, freshly distilled,** sterilized water and **injected very slowly.**

Initial dose for men 0.2 or 0.3 gram salvarsan or 0.3 or 0.45 gram neosalvarsan; for women, 0.2 gram salvarsan or 0.3 gram neosalvarsan.

Subsequent doses for men 0.4 to 0.6 gram salvarsan or 0.6 to 0.9 gram neosalvarsan; for women, 0.4 or 0.5 gram salvarsan or 0.6 to 0.75 gram neosalvarsan.

Mercury

Soluble—bichlorid: from ¼ to ½ grain injected in the buttock three times a week, if possible.

Insoluble—salicylate: 1 grain injected into the buttock once a week.

Urine should be examined at frequent intervals to ascertain the presence of any renal irritation caused by the mercury.

Iodides

Begin with 10 drops saturated solution three times a day in water or milk, increase so that the patient is taking from 100 to 125 grains three times a day when the occasion requires.

Courses of Treatment

Salvarsan or neosalvarsan to be given at from 5 to 7 day intervals until eight injections have been administered. Mercury to be administered for twelve weeks; three times a week in the soluble form, if possible, and once a week in the insoluble form.

Iodides to be administered when syphilitic gummata are present, in latent syphilis, and in syphilis in which the nervous system is involved.

After one course the patient to rest for four weeks and then a Wassermann taken.

If positive, a second course is necessary and subsequent courses depend upon the condition of the Wassermann.

If negative, a Wassermann to be taken at monthly intervals for a year, after which they should be taken at least quarterly over a long period.

Before pronouncing a patient cured, there should also be a persistent negative Wassermann of the spinal fluid.

General Treatment

It must be remembered that syphilis is a constitutional disease and the patient is very likely to require other than antiluetic treatment. On account of the destruction of the red blood corpuscles by the inroads of the disease, tonics are usually demanded. For emaciation, cod liver oil is recommended; for anemia, iron; and, for the stimulation of general nutrition as well as the nervous system, strychnin is advised. Tincture of

THE INTRAMUSCULAR INJECTION OF MERCURY

After the mercury has been slowly deposited in the muscles, the needle is withdrawn, the parts thoroughly massaged and the point of needle entrance sealed with collodion.

nux vomica is also a tonic which works to advantage in syphilis, particularly when combined with tincture of cardamom comp. and glycerin.

The patient's weight should be observed from time to time and the condition of the blood should also be watched by means of the hemoglobinometer.

Many patients do well under a Turkish bath, without the cold plunge, once or twice a week. This aids in elimination and is of particular assistance in those cases in which the mercury may be slow in leaving the system.

Hydrotherapeutic Treatment

In addition to the hygienic treatment of the syphilitic as laid down in another chapter, the hydrotherapeutic form of treatment should not be overlooked when patients can afford such. The various hot springs of the country offer specific methods of hydrotherapy which are undoubtedly beneficial. Patients who are not able to go to hot springs for treatment of this nature are often benefited by the baths at such resorts as Saratoga Springs. There is nothing at Saratoga which can be claimed to possess curative properties, but patients who are sent there are given the eliminating treatment with carbonated baths at the Lincoln Bath House at temperatures varying from 97° to 110°. In alternation with these baths, the electric cabinet baths with a fan spray following, for reaction, are employed. Very satisfactory results have been observed when this line of treatment has been carried out in conjunction with the usual anti-luetic treatment.

CHAPTER X

REACTIONS AND ACCIDENTS FOLLOWING THE USE OF ARSPHENAMINE

Reactions

Sometimes during an injection of arsphenamine or neoarsphenamine certain phenomena will be noted which have been termed nitroid crises. These include nausea, malaise, flushing of the face, headache, precordial distress and dyspnea, and are usually inconsequential. Being of an anaphylactoid type, they can be relieved by the intramuscular injection of from ten to twenty minims of a 1:1000 solution of epinephrin. When patients are known to exhibit such symptoms, difficulty can be obviated by the injection of the epinephrin ten minutes before the anticipated injection of salvarsan.

Dr. J. H. Stokes of Rochester, Minn. (*J. A. M. A.*, Jan. 25, 1919) observed that the epinephrin administers a shock to the system by its powerful vasomotor action and states that he has "seen occasions in which patients have for the moment seemed in as much risk of serious damage from the therapy as from the original arsphenamine reaction."

Dr. Stokes thereupon set out to discover a method which should protect his patients against reactions following the use of arsphenamine and to support his view that such a reaction is a manifestation of anaphylactic shock. He sought, in other words, an anti-anaphylactic agent. For this purpose he utilized atropin, which has an inhibitory effect.

It was first employed in the case of a woman whose intolerance to neoarsphenamine was beyond doubt. Suffering from a florid follicular secondary syphilid, the initial moderate dose was followed by a rather sharp Jarisch-Herxheimer reaction, and, during her first course of five injections, she gave abundant evidence of gradually increasing intolerance to the drug.

Six weeks later the administration of 0.3 neoarsphenamine was followed in two minutes by an intense scarlet flush and edema of the face and neck, with cough, stridor and vomiting. A subcutaneous injection 10 minims of 1:1000 of epinephrin restored her completely.

A week later the woman was given 1/50 grain of atropin hypodermatically and fifteen minutes later received 0.6 neoarsphenamine, with only a slight reaction, and at the period of the third injection the following week the use of atropin permitted the injection of 0.7 gram with only distinct nausea as a disagreeable factor.

Successful Employment of Atropin

At a later period, deciding to produce, if possible, antianaphylaxis by atropin, Dr. Stokes gave the woman intravenously 0.05 gm. of the drug in 0.5 c. c. of water. He goes on to say:

"The neoarsphenamine used was of the same control number as that employed for the previous injection, which had shown itself capable of producing marked reaction in this patient (Control V U J). Following the injection of the half decigram dose, the patient became slightly dizzy and was a trifle nauseated on returning to bed. One hour after the preliminary injection the patient received 0.55 gm. of neoarsphenamine intravenously in concentrated solution, injected at the usual rate. The complete inhibition of all reaction was striking. There was no flush, no nausea nor vomiting, no dizziness, cough nor stridor. The eyes became slightly suffused. The patient felt so much better than usual as to astonish her and all those who knew of her reactions. She was returned to her room, and no reaction was reported for twenty-four hours. At the end of this time, without rise of temperature or any other marked systemic symptoms, a generalized macular erythma of the typical late toxic type appeared. It was not accompanied by constitutional symptoms and disappeared two or three days later. It was judged wise, however, not to invite an exfoliative dermatitis by any further arsenotherapy."

Dr. Stokes comments further on the matter:

"This case was surrounded by all the precautions against pseudoreaction that we could devise. The reactions observed were typical of the acute nitritoid crisis and we felt that the sequence of events, as described, had not been modified by presuppositions on the part of the patient or by hysterical manifestations. Abundant objective evidence of the patient's intolerance was available. Not the least interesting suggestion based on these observations is the possibility that the acute anaphylaxis and the delayed toxic erythema are different types of reaction. An antianaphylaxis which was developed to protect the patient against the former failed to protect against the latter complication. The influence of atropin seemed to be quite definitely a function of the dosage, and doses below 1/50 grain failed to protect the patient against shock.

"Since its successful employment in the case described, we have resorted a number of times to the induction of antianaphylaxis as a protection against acute arsphenamine reaction, notably in the treatment of patients with tuberculids, who show an idiosyncrasy in about 50 per cent of the cases. I have noted with interest Danysz' impression, which my experience confirms, that small preliminary injections 'vaccinate' the susceptible patient, so to speak, against the larger doses, an observation which Danysz supports by animal experiment, and offers likewise as a rationale for the regulation of dosage in treatment, and a means for increasing individual tolerance of the drug."

Summary of Stokes' Conclusions

"The acute 'nitritoid' crisis or reaction to arsphenamine is a form of anaphylactic shock, explainable on physicochemical grounds as the result of a precipitation either of the drug from its colloidal solution, or of the colloids of the blood plasma, by the drug, or by an impurity. The reaction following the injection of an acid or only partially alkalinized solution of arsphenamine either too rapidly or in too high concentration is presumably of the same type.

"The nitritoid crisis can apparently be inhibited by a previous injection of atropin (1/50 grain), which further suggests that the reaction is a form of anaphylactic shock.

"The induction of antianaphylaxis as described above further supports the belief that the nitritoid crisis is a form of anaphylactic shock.

"The induction of antianaphylaxis in patients exhibiting persistent idiosyncrasy to arsphenamine or neoarsphenamine has proved clinically useful, and, as a means of increasing their tolerance of the drug, deserves further trial and study."

Reactions from Faulty Technic

In a very small percentage of cases a temperature may be noted, sometimes running as high as 103°. This may or may not be accompanied by pain, nausea, vomiting and purging. These cases were especially prevalent several years ago when too little attention was paid to the gastro-intestinal tract and to the freshness of the distilled water and the sodium hydroxid.

Rest in bed, pyramidon, acetyl-salicylic acid and liquid diet will promptly restore these cases.

Care should be observed in subsequent administrations, the dose should be smaller and these patients should be given atropin, following the ideas of Stokes, as hereinbefore set forth. Epinephrin given hypodermically will usually control the unpleasant after-effects of acute reactions.

Some Late Reactions

Among the late reactions are dermatitis and erythema, sometimes accompanied by renal disturbance. A nephritis may also occur without any of the noticable dermatological conditions.

Icterus occasionally follows the administration of arsphenamine. Much trouble was experienced in France with the French arsphenamine and so much jaundice occurred in England during the war that special studies have been undertaken to locate the cause and determine a cure.

Whenever chemicals containing ring compounds reach the

blood stream, certain decompositions take place yielding compounds of simpler structure which in turn cause a marked increased destruction of red blood corpuscles. These changes take place in from two to twelve hours and they in turn change the bile secretion, due to the clogging of the fine bile ducts and followed by inflammatory and hemorrhagic conditions.

This happens when there is a hemolysis in the blood stream and this is one of the objections to the use of concentrated arsenical solutions. In addition dermatitis exfoliativa may follow the use of the concentrated solution. Dr. C. N. Myers, U. S. Public Health Service, has demonstrated this last statement in about 1,000 cases, using the same material for the more dilute solutions as well as for the concentrated solutions. The dermatitis occurred frequently with the concentrated solutions and not a single case in the more dilute.

The Herxheimer Reaction

Another very rare symptom is the Herxheimer reaction. The liberation of endotoxins may cause symptoms of pressure, or some impairment of function. The Herxheimer is ordinarily noticed in connection with beginning brain lesions, although reactions of a similar nature occur when lesions of the circulatory system or of the viscera are present.

Great care should be exercised in the use of arsphenamine in cases such as described, and it is well to employ mercury or the iodides freely and for several days before the administration of salvarsan. Careful physical examination will guard against trouble in this connection.

Nerve Disturbances

Other so-called reactions are disturbances of the ocular, auditory and other nerves. These are generally indications of the activities of the syphilitic lesions and demonstrate the necessity for further arsenical treatment. For example, Benario observed an involvement of the auditory nerve in 62 cases out of 14,000 treated by him with salvarsan. The deafness was tem-

porary and disappeared as soon as the antisyphilitic treatment was discontinued.

Jacobsen (*Ugesk. for Læger*, Copenhagen, March 13, 1919) discusses four cases of syphilis in the auditory nerve or labyrinth in which sudden deafness, ear noises or vertigo and vomiting were the symptoms of reaction, showing that lues had invaded the ear or that the drugs had caused a reaction. He says (*J. A. M. A.*, May 10, 1919) "analysis of these and similar cases on record seems to show that part of the neurorecurrences are due to a Herxheimer reaction to arsphenamine. This reaction congestion in a nerve confined in a narrow passage through bone injures the nerve and may cause permanent trouble. But the majority of cases of disturbances in the auditory nerve are the result of actual damage from the syphilis, combined with or possibly secondary to a syphilitic meningitis. There may possibly be also a small contingent of cases in which the nerve is suffering from a direct toxic action from the arsphenamine. Even in persons with normal ears, special care should be exercised in giving arsphenamine; during the exanthem stage or a little before this, it is wiser to give the arsphenamine only in combination with mercury."

Very occasional symptoms, which are designated under the anaphylactic group, are coryza, sore throat, urticaria, indigestion and diarrhea, but they are as fleeting as they are uncommon.

The Causes of Reactions

Without doubt, there are numerous causes for reactions.

Wassermann blames the bacterial proteins in the water; Wechselmann, the rapid dissolution of great quantities of spirochetes and the freeing of their constituent parts. Some ascribe reactions to the "setting free of some toxic substances from the spirochete," or to the "liberation of endotoxins from the killed organisms," or to impurities in the drug itself.

Without doubt, each reason is tenable and reactions might be caused even by two of the reasons ascribed acting simultaneously. We are convinced, however, after a large experience in the administration of arsphenamine, that the febrile and gastro-

intestinal disturbances which may follow the injection will be found due to one or more of these causes:

(a) Dissolving the arsphenamine in warm or in hot water.

(b) Failure to use fresh double distilled water.

(c) Too hurried introduction of the solution into the circulation.

(d) Failure to dissolve thoroughly the arsphenamine in water before adding the salt solution.

(e) Adding the sodium hydroxid solution after the salt solution has been mixed with the arsphenamine solution, instead of before, thus producing a turbid solution.

(f) Failure to use the sodium hydroxid in the proper proportions and manner.

(g) Failure to filter the completed mixture before using.

(h) Using gauze for filtering purposes that contains shreds which pass through with the mixture.

(i) The use of impure chemicals.

(j) Failure to prove that the arsphenamine solution was sufficiently alkaline.

(k) A cracked ampule, permitting the access of air and a consequent oxidation of the drug.

(l) Unclean apparatus.

(m) Piercing the wall of the vein on the side opposite to the needle's point of entrance, thus infiltrating the tissues with the mixture, and causing local disturbances.

(n) Using an excessive dose, or too frequent administration of large doses.

(o) Too long delay after preparation in using the mixture.

(p) Idiosyncrasy of the patient against arsenic preparations.

(q) Non-recognition of the physical condition of the patient, who may have had a disease or diseases which contraindicate the uses of arsenic compounds.

Summarized, imperfections in the technic of the operator or his failure to prepare properly his patient for treatment with arsphenamine.

Undue Caution may be Harmful to Patient

Many physicians are unduly cautious regarding the so-called

reactions occurring during salvarsan injections, and interpret minor symptoms so seriously that the patient is oftentimes needlessly denied the benefit of arsphenamine treatment because of the over-anxiety of the administrator.

We have seen physicians stop an injection the moment a slight flushing of the conjunctiva was observed. In some instances flushing is premonitory of trouble, but generally such a sign possesses no significance.

If the operator will watch the heart through the pulse he will have an excellent guide to his further procedure.

In initial cases the pulse may go to 100 or even higher owing to the nervousness of the patient and the sting from the introduction of the needle, but when the patient is reassured it shortly resumes its normal rate. In a recent series of 100 cases with one or more injections there was practically no variation in the pulse rate sufficient to cause the slightest unrest on the part of the physician.

The Importance of Heavy Dilutions and Slow Injections

We have urged for several years in our writings on syphilis and its treatment by salvarsan and mercury, that the technic of preparation and administration as laid down by the discoverer of the drug should be employed.

Unfortunately too many physicians have attempted to improve on the technic, with the result that the patient is ofttimes the sufferer.

We have laid especial emphasis on heavy dilutions and the necessity for slowness of entrance of the well-diluted drug into the circulation. We have also strongly advised the immersion of the salvarsan ampules in 95 per cent alcohol, so that any minute crack in the glass may be detected. Cracks hardly visable to the naked eye permit oxidation, and if undiscovered, cause consequent reactions. Many physicians have immersed the ampules in water, but the size of water molecules is too great to permit of entrance through very minute cracks.

It is a pleasure, therefore, to observe that the United States Public Health Service, through the capable director of its Hy-

gienic Laboratory in Washington, Dr. George W. McCoy, has publicly directed attention to the absolute necessity of carrying out these important details. He makes a statement which many of us have believed and preached for years, that "any physician who fails to observe these precautions should be considered as directly responsible for serious results that follow the improper use of the drug."

U. S. Public Health Service on Concentration and Rapidity of Administration

A few feeble voices in the wilderness avail little, but a voice speaking with authority is clearly heard over the clamorous tumults of the multitude. The profession has every reason to congratulate itself that Dr. McCoy has directed the attention of arsphenamine users, present and prospective, to the absolute imperativeness of careful and proper technic, and, unless all signs fail, it will not be long before the reactions following arsphenamine injections will be but a memory.

Dr. McCoy made known his dictum through a letter published in the weekly medical journals of May 10, 1919, which reads:

"It appears that there is a lamentable want of care on the part of many physicians who administer arsphenamine as to the concentration of the drug used and the time required for administration.

"The Hygienic Laboratory receives many complaints in regard to untoward results from the administration of arsphenamine made by various American producers. When careful investigation is made it is almost invariably found that the drug has been used in a solution that is too concentrated, and that it has been administered too rapidly. We have reports of a dose of 0.4 gm. being given in a volume of as little as 25 c. c. and injected within thirty seconds. Such practice is abuse, not use, of a powerful therapeutic agent.

"If, in addition to the usual precautions as to the use of perfect ampules and neutralization, physicians would give the drug in concentration of not more than 0.1 gm. to 30 c. c. of fluid and

allow a minimum of two minutes for the intravenous injection of each 0.1 gm. of the drug (in 30 c. c. of solution) the number of reactions would be very materially reduced. This would necessitate from 30 to 180 c. c. of the solution for the doses usually given and would require from six to twelve minutes for the injection.

"Any physician who fails to observe these precautions should be considered as directly responsible for serious results that follow the improper use of the drug."

The *Journal of the American Medical Association*, under the caption "The Administration of Arsphenamine," had this to say editorially (p. 1372):

"Elsewhere in this issue appears a letter from Dr. George W. McCoy, director of the hygienic laboratory of the United States Public Health Service, concerning two special points in the administration of arsphenamine, namely, the dilution and the rapidity of administration. His letter is followed by a circular issued by the Public Health Service to all its officers covering the same general subject. Numerous disagreeable results following the use of the various preparations of arsphenamine have led research workers to make a special study of the cause of these accidents. Such studies have indicated that most of the disagreeable results are not inherent in the preparations themselves, but are produced through faulty steps in the administration of the remedies. The suggestions made in the circular of the Public Health Service, if followed by physicians, will aid in preventing repetition of disagreeable after effects."

The *Journal* appends this note to Dr. McCoy's letter:

"The United States Public Health Service has issued a circular to its officers concerning the proper mode of administering these preparations. It is appropriate to reproduce this circular in connection with the letter of Dr. McCoy. Careful attention to the letter and the following points from the circular mentioned will undoubtedly reduce the number of reactions following the use of arsphenamine preparations."

The circular issued by the United States Public Health Service to its surgeons is presented herewith:

ADMINISTRATION OF ARSPHENAMINE AND NEO-ARSPHENAMINE

TREASURY DEPARTMENT

Bureau of the

United States Public Health Service

Washington, April 28, 1919.

Bureau Circular
Letter No. 163.

Medical Officers, U. S. Public Health Service,
and others concerned:

In view of the variations of technique of the administration of arsphenamine and neo-arsphenamine at various Service clinics, attention is invited to the following points, careful observation of which should reduce the number of reactions from the use of this drug.

The ampule, before opening, should be immersed in 95% alcohol for fifteen minutes, so as to detect any crack or aperture not primarily recognizable. (Should such a breach be discovered, the contents of the ampule should be discarded.)

ARSPHENAMINE

(1) Solution: Cold, boiled, freshly distilled water should be used in all cases except in the case of "arsenobenzol" made by the Dermatological Research Laboratory, in which case hot water is required. No more solution should be prepared at one time than can be given in 30 minutes.

(2) Neutralization and alkalinization of the above solution: With a graduated pipette or burette add 0.9 cc. of Normal NaOH for each 0.1 gm. of the drug (*i. e.*, 5.4 cc. for each 0.6 gm.). The alkali should be added all at once and should quickly convert the acid salt solution of arsphenamine into the alkaline salt solution, or the disodium of salt of the arsphenamine base. The solution of arsenobenzol, which is hot, should be cooled before adding the alkali. This represents slightly more alkali than just enough to re-dissolve the precipitate formed by the addition of this reagent.

The alkali used should be standardized against normal acid. Normal NaOH is a 4% solution of the c. p. product. However, if made on the basis

of weight, it may be considerably less than this strength, hence the necessity for titration. It could be made up in amount sufficient for a month's use, if kept in a well-stoppered bottle and exposed to the air for only a few seconds at a time when using the solution. It should be kept in a bottle that has been used for NaOH solution for some time so that all action it might cause on the glass has already occurred. Where it is impossible to have this made up at the station, it will be furnished upon request from the Hygienic Laboratory. Should the NaOH solution become cloudy or contain a precipitate, it should be discarded.

(3) Concentration of the Drug: It is desired to emphasize the fact that the concentration of the drug should not be greater than 0.1 gm. to 30 cc. of final solution. The practice of using concentrated solution is not only in direct conflict with the instructions on the circular, but carries a distinct hazard to the patient.

(4) Method of Injection: The gravity method only should be used. Where several patients are to be injected from the same solution, the container of the solution should be graduated. If not already graduated, this can be done in a few minutes by sticking on a strip of adhesive plaster and marking the graduations on this. A convenient way to do this is to have each mark represent 30 cc. with a long mark for each 180 cc.; then, if the volume is made up so that each 0.1 gm. of drug is contained in each 30 cc., the doses can be given accurately. It is a great convenience to have a glass stop-cock near the glass tubing which serves as a window just above the needle in order to control the rate of injection. If no stopcocks are at hand, the rate can be controlled by the size of the needle and the height of the column of fluid. A No. 18 or 20 B. & S. gauge is the best size needle.

(5) Rate of injection: Operators should pay particular attention to the rate of administration and in no case exceed 0.1 gm. of drug (30 cc. of solution) in 2 minutes. This point is especially emphasized because it is believed that excessive rapidity of administration accounts for more unfavorable results in the use of arsphenamine than any other one thing.

NEO-ARSPHENAMINE

The principal precautions to be observed in the administration of neoarsphenamine are:

(1) But a single ampule should be dissolved at a time. This drug must not be dissolved in bulk to be given to a series of patients.
(2) Cold water only should be used.
(3) The dilution should be not stronger than 0.1 gm. of the drug in 2 c. c. of freshly distilled water.
(4) A very small needle should be used, and the time of injection of the dose should be not less than five minutes.

CAUTION

Operators are advised that they will be held responsible for untoward results following the use of arsphenamine and neo-arsphenamine in cases where there has been material deviation from the outline given above.

Acknowledgment of receipt of this letter is directed.

Respectfully,

RUPERT BLUE,

Surgeon General.

Accidents

Serious accidents practically never follow the proper introduction of a properly prepared arsphenamine solution into the circulation, *i. e.*, when the physician's technic is perfect. There is no reason why perfection should not be attained, particularly when we consider that faulty technic endangers human life.

A common accident is the penetration of the vein at a point opposite the proper place of entrance of the needle. As a result, the solution leaks into the surrounding tissue and the infiltration may develop a badly inflamed arm and a possible abscess with sloughing. Such an occurrence can be obviated by using a short beveled needle, and by first introducing sterile distilled water into the vein, until the operator is certain the flow is free and the needle properly in the vein.

Acidity of the solution may bring about a phlebitis, with its attendant difficulties.

Over-alkalinity of the solution may result in the formation of a thrombus, which will enter the circulation. Wounding of the vein may also cause a thrombus.

Dr. Loyd Thompson of Hot Springs, Arkansas, reports (*Syphilis*, p. 238, 1916) the case of a physician who, finding that the blood did not flow freely through a needle inserted in an elbow vein, opened up the lumen of the needle with its stylet. A blood clot was undoubtedly pushed out of the needle into the vein, as the patient died before the solution was administered.

Embolism may also follow the introduction of air into the vein on account of the failure of the operator to drive all the air out of the cylinders and tubing.

Embolism may be caused by bits of cotton which enter the solution while it is being filtered.

The Importance of Watching the Kidneys

Patients have died during or soon after the administration of arsphenamine. We believe that in the majority of instances the fault is that of the operator, in that some important essential was overlooked. A physical examination of the patient, often neglected, might have revealed some contraindication.

Urinary examinations are too seldom made by many physicians administering arsphenamine, who, forgetting this essential, can only trust to good fortune that the kidneys of their patients are in the proper condition to eliminate the arsenic.

Dr. E. L. Keyes, Jr., of New York (*Urology*, p. 829, 1917) is of the opinion that acute congestion of the kidneys is the most common cause of death. He gives acute encephalitis as another *casus morti*.

He advocates a careful examination of kidneys and urine, and advises that if the urine reveals albumin and casts and if it shows a deficient excretion of urea the physician inject only a third or a fourth of the usual dose of arsphenamine.

Col. E. B. Vedder, U. S. Army (*Syphilis and the Public Health*, p. 287, 1918) lays particular emphasis on the condition of the kidneys at the time of treatment. He notes that in fatalities occurring in patients in the active secondaries two or three days after the injection, they presented symptoms resembling uremia. He observes that in three and one half years four fatalities occurred in over 31,000 injections and that three of the four cases on autopsy revealed an intense acute nephritis.

Wechselmann (*The Pathogenesis of Salvarsan Fatalities*, St. Louis, 1913) believes that some deaths following the use of salvarsan are due to previous injuries by mercury to the kidneys, which are thus unable to eliminate the arsenic.

Animal Experiments Reveal Interesting Facts

Fatalities follow in an exceeding small percentage of cases. The percentage is, doubtless, between 1/50 and 1/100 of 1 per

cent, a number almost negligible. Such a factor must, however, be considered, and we are, therefore, interested in some of the animal experiments of D. E. Jackson and M. I. Smith of the Division of Pharmacology of the Hygienic Laboratory, United States Public Health Service. (*Jour. Phar. and Exper. Therap.*, Vol. XII, No. 4, 1918.) They made an analysis of the effects of various arsphenamine preparations on the cardio-vascular apparatus for the purpose of ascertaining the cause of acute reactions, and examined various remedies in the search for an efficient method of treating acute collapse from the drug.

Alkaline solutions were used. When a dose, averaging the amount usually used in the clinic at the Hygienic Laboratory, was injected slowly there was little or no immediate cardio-vascular change observed, but acceleration of the injection rate and an increase in the dose produced definite effects. The first of these was a slight but gradually progressive dilatation of the heart and a slow fall of blood pressure.

A rapid injection, it should be noted, is likely to cause a rather marked, sudden fall of blood pressure.

Large doses of arsphenamine caused a variety of vascular reactions of the internal organs, such as dilatation of the spleen, contraction of the kidney and dilatation of the intestinal vessels.

Further experimentation demonstrated that if a dose of 30 mgm. per kilo of a 2 per cent arsphenamine solution were injected in a dog rapidly, *i. e.*, within three or four minutes, the pulmonary blood pressure might be increased 100 per cent or more and a marked fall in systemic blood pressure was likely to occur.

The authors feel that under the unusual conditions under which the heart must work when enormous rises in pulmonary blood pressure are produced by large doses of the drug, the heart may be so strained that delirium cordis may well be expected.

They are of the opinion that the alkalinity of the arsphenamine solution alone may be responsible for a considerable degree of rise in pulmonary blood pressure, but they also believe that the specific action of the arsenic compound is responsible for part and may be most of the increase in pulmonary arterial tension.

They emphasize the fact that rise in pulmonary pressure was observed only when large doses of the drug were injected.

They further state that, while large doses of concentrated alkaline solutions rapidly injected always produced marked rises in pulmonary blood pressure, slow injections of dilute solutions brought about no visible rise in pulmonary pressure.

Important Rôle Played by Disturbance of Pulmonary Circulation

Jackson and Smith are, therefore, led to the belief that a disturbance of pulmonary circulation is one of the chief factors when patients complain of faintness, dyspnea and circulatory disturbances.

Moderate doses of a good arsphenamine preparation slowly injected produced but little effect on the respiration, but as the action of a large dose developed the respiration became slower and shallower.

Respiratory embarrassment is the result of depression of the respiratory center and of a greatly depressed circulation. Artificial respiration proved of no avail.

In experimental arsphenamine intoxication, Jackson and Smith found that respiratory failure was probably the immediate cause of death, as the heart usually beat a short time after breathing ceased.

If a rapid injection of a toxic preparation was given frequently the heart and respiration stopped simultaneously.

The experimenters, in their search for the trouble-making properties, carefully went into the effects produced by the intermediary and oxidation products which are formed in the process of manufacture of arsphenamine, but they were satisfied that none of these play a significant rôle in acute toxic action.

Danysz (*Ann. de l'Inst. Pasteur*, Paris, No. 3, p. 114, 1917) believes that arsphenamine in alkaline solutions may undergo precipitation in the blood stream, thus forming insoluble masses which tend to lodge in the smaller blood vessels, especially in the pulmonary vessels, thus giving rise to serious symptoms. He thinks that later these insoluble masses again undergo solution, due to the solvent action of the blood and tissue juices, which,

combining with the masses of arsphenamine, form soluble, organic compounds which are carried by the blood stream to the tissues of the body.

Jackson and Smith endeavored by a series of experiments to corroborate this theory, but without success. They found the toxicity of arsphenamine was not effected, nor could they demonstrate with alkaline solutions that precipitation and embolism occurred.

The Use of Tyramine in Cases of Collapse

For the treatment of acute arsphenamine collapse Jackson and Smith suggest tyramine (parahydroxyphenylethylamine) which can be given intravenously in time of emergency or intramuscularly or subcutaneously. They say they have prolonged the lives of animals severely poisoned with arsphenamine by introducing intravenously 10 mgm. of tyramine into animals weighing from 5 to 10 kilos. The drug stimulates the heart and produces a prolonged and sustained rise in systemic blood pressure. The effects of tyramine progressively decrease after the initial rise in pressure, which requires from one to five or more minutes for its full development. The investigators say the systemic pressure does not rise so high and the danger of acute dilatation of the heart is not so great as with the intravenous injection of epinephrin, but the effects of tyramine are much more lasting.

Hewlett (*Arch. Int. Med.*, XXI, 411, 1918) has injected tyramine hypodermically in doses of 40 to 80 mgm. with an average of 60, and has been satisfied with it as a blood-pressure raising agent. It also seems to improve the circulation.

The consensus of the best opinion is that few fatalities result from the toxicity of the arsphenamine itself but that the results usually come from imperfection in technic, physical inability of the patient to assimilate arsenic or metabolic changes in the system not as yet understood by physiologists.

CHAPTER XI

THE WASSERMANN REACTION AND THE EFFECTS OF TREATMENT THEREON

The Provocative Wassermann Reaction

After a luetic patient is believed to be free from the spirocheta pallida it is the practice of most syphilologists to give a provocative injection of salvarsan. Gennerich (*Ber. Klin. Woch.*, 1910, No. 38) reported that negative Wassermann reactions often changed to positives after a salvarsan injection. Thus we are able to demonstrate the effectiveness of our treatment by a provocative injection.

Our procedure is to inject 0.3 salvarsan intravenously and have a Wassermann done every day thereafter for six days, by which time the change of the reaction will be effected, if there is any cause to change. It is well, however, to have Wassermanns also done on the 8th, 10th, 12th and 14th days after the provocative injection, as the reaction may be unduly delayed.

If spirochetæ are in the system their presence will probably be made known by this method. If a negative Wassermann remains negative after a provocative injection, and all other standards are fully met, we have a right to conclude that the patient is cured. (See pp. 152–153.)

Drs. John H. Stokes and Paul A. O'Leary of the Mayo Clinic in an enlightening paper on this subject (*Am. Jour. Syph.*, i, 629, 1917) presents these indications for the provocative injection:

"1. A definite history of primary or secondary lesions or a suspicious genital sore of any description. (With a negative Wassermann.)

"2. Syphilis in husband or wife or a history of a sore in either.

"3. Treated cases to determine the fact of cure or need for further treatment. One-third of the cases thus tested by us, gave a positive provocative effect.

"4. Obscure bone or joint lesions.

"5. Histories of miscarriages unless the anatomical cause is glaringly obvious.

"6. Mothers of syphilitic children without clinical signs of the disease.

"7. Cases with a history of a positive Wassermann elsewhere, negative on present examination.

"8. Mental deviates and constitutionally inferior individuals with suspicious histories.

"9. Certain signs elicited by special examinations, such as decreased bone conduction with normal hearing, chorioretinitis and retinitis pigmentosa, bilateral dacryocystitis in childhood," etc.

The Effect of Arsphenamine and Mercury upon the Wassermann Reaction

A careful study of the literature upon this subject since salvarsan first appeared shows the effect of the fallacious belief that one injection will completely kill all the treponemata and cure the patient. In the earlier days many cases relapsed within a year because mercurial treatment had not been used in conjunction with salvarsan or on account of too little treatment.

Today, when we realize that the system must be flooded with anti-luetic agents, the number of cases relapsing has been reduced to a minimum.

In acute cases, treated before the Wassermann has become positive, we are usually able to keep it negative if vigorous treatment is employed.

In acute cases in which the first examination reveals a positive reaction, regular salvarsan treatments and mercury injections generally change the positive to a negative in from four to eight weeks.

When primary cases are treated, as is our custom, with eight injections of arsphenamine, at from five to seven day intervals, and with mercurial injections or inunctions for twelve weeks, the chances strongly favor a continuous negative reaction, unless something unforeseen occurs.

In cases of long standing, several courses may be necessary to change the reaction. One of our cases, a man sixty-four years old, with a history of luetic infection twenty-one years before presenting himself to us, took seven courses, with the usual amount of mercury, before a negative reaction was obtained. The subsequent results, however, justified this persistent effort.

The consensus of opinion is that conjoint arsphenamine and mercury treatment, faithfully and intelligently administered, will usually produce a negative reaction in primary positive cases in two months or less, and that in long-standing cases consistent treatment will eventually bring about a permanent negative in a majority of cases except in those aortic or cord lesion cases, which are irresistible to treatment from a serological standpoint.

The Definite Serological Effect of Arsphenamine

Many years must necessarily elapse before we can say with absolute certainty that salvarsan and mercury have a real definite and lasting action upon the Wassermann reaction.

We know the action of mercury as a medicinal agent, for it has been utilized as an antiluetic for centuries.

Since the Wassermann reaction became known the medical profession has had ample opportunity to study the effect of mercurial treatment in connection with that reaction.

It is, however, too early to make affirmative statements regarding salvarsan's permanent effacement of the positive Wassermann.

Experience has taught us that mercury has not been the effective spirocheticide that our medical forebears considered it. Relapses under mercury were not uncommon. Many an unfortunate syphilitic was lulled into security by the disappearance of outward symptoms under mercury and its accompanying medication, only to awaken after a period of years to the horrible realization of tabes, paresis and other sequelæ which are the results of an invasion of the treponemata.

We indulge the hope that salvarsan produces a more permanent effect on the system and that relapses will be less com-

mon following its proper use, but sufficient time has not elapsed to verify this hope sufficiently to make it an undisputed fact. However, as Col. Charles F. Craig, U. S. Army, well says, it has been demonstrated that in the treatment of lues mercury is of small value, when compared with salvarsan.

He states (*The Wassermann Test*, 1918, p. 184) "for one case that becomes negative after treatment with mercury there are hundreds that become negative after treatment with salvarsan, and although the majority of both classes of cases relapse in time and again present a positive Wassermann reaction, the relapses are much less frequent among patients treated with salvarsan than with mercury."

Positive Results from Salvarsan and Mercury

The effect of salvarsan and mercury upon the Wassermann reaction is not, fortunately, a matter of conjecture.

The work of Craig and of other careful observers has proved that we have something real to look forward to as a result of the combination of these two antiluetics. Craig (*ibid.*) continues:

"The relative efficiency of salvarsan and mercury in causing a disappearance of the Wassermann reaction is well illustrated in patients who had previously been treated with mercury before receiving salvarsan. Of 90 patients who were treated with mercury by the mouth for nine months or more before the administration of salvarsan and who gave a positive Wassermann reaction, 68, or 70.5 per cent became negative within eight weeks after the administration of the drug. The intensity of the reaction at the time of receiving salvarsan and the length of time the patients had been taking mercury is shown in this table:

THE WASSERMANN TEST IN PATIENTS WHO HAD TAKEN MERCURY FOR VARIOUS PERIODS OF TIME (AFTER CRAIG)

Method of Treatment	*Time of Treatment*	*Number of Cases*	*Character of the Reaction*		
			++	+	+−
Mercury by mouth	9 months	17	8	7	2
" " "	1 year	26	16	8	2
" " "	2 years	17	7	9	1
" " "	3 years	8	3	4	1
Totals		68	34	28	6

"The table shows that 26 of these patients had taken mercury by mouth for a period of one year and that 16 of them still gave a four plus reaction; that 17 had received the same treatment for two years, of whom 7 still gave a two plus reaction; and that 8 had received treatment for three years, of whom 3 still gave a two plus reaction. Of the 68 cases not one had become negative as the result of mercury administered by the mouth, but after the administration of salvarsan every one became negative within 8 weeks. This is certainly very decisive proof of the greater specific action of salvarsan and could only be ascertained by the effect of the drugs in question upon the Wassermann reaction.

"Objection may be raised to the results recorded above by calling attention to the fact that the administration of mercury by mouth is now well recognized to be the poorest of all ways of giving this drug, although it is not so long ago that three years' treatment by mouth with mercury was considered by the best authorities upon the disease as adequate for the cure of syphilis. In answer to this objection another table is given, covering 18 patients treated with hypodermic injections of mercury, a plan of treatment generally acknowledged to be the most efficient of the many ways of administering the drug. For purposes of comparison the effect upon the Wassermann of treatment with salvarsan is also included.

THE COMPARATIVE RESULTS OF TREATMENT WITH MERCURY AND SALVARSAN UPON THE WASSERMANN REACTION (AFTER CRAIG)

Number of Cases	MERCURIAL TREATMENT		SALVARSAN TREATMENT	
	Injections of Gray Oil	*Character of Reaction*	*Dose 0.6 gm.*	*Character of Reaction*
2	7	++	Intramuscular	—
1	8	+	" "	—
1	9	++	" "	—
1	11	++	" "	—
3	15	++	Intravenous	—
1	15	+	Intramuscular	—
4	18	++	" "	—
2	19	++	Intravenous	—
1	20	++	" "	—
1	25	+	Intramuscular	—
1	30	+	" "	—

"From a consideration of this table it is evident that cases having had as many as 18 to 20 injections of gray oil still gave a two plus Wassermann reaction and that cases having as high as 25 and 30 injections still gave a three plus reaction. After the administration of salvarsan all became negative within 8 weeks, and in 12 of the cases only one intramuscular injection of 0.6 gm. of salvarsan was administered. While there is reason to believe that previous treatment with mercury may have had something to do with the good effects produced by salvarsan upon the reaction, it must be admitted that the results obtained in these cases demonstrate beyond all question the superior specific value of salvarsan upon treponema pallidum.

"Patients who have been previously well treated with mercury show a higher percentage of negative results after treatment with salvarsan than those who have received no mercurial treatment. Thus of 75 patients who had received mercurial treatment before receiving salvarsan, 84 per cent became negative, while of 110 patients who had received no treatment before the administration of salvarsan, only 74.5 per cent became negative.

"In order to illustrate the persistence of the positive Wasser-

mann reaction after treatment with mercurials, another table has been prepared giving the method of treatment, the length of time the patient was under treatment, the number of cases observed, and the intensity of the reaction.

ILLUSTRATING THE PERSISTENCE OF THE WASSERMANN REACTION AFTER TREATMENT WITH MERCURY (AFTER CRAIG)

Method of Treatment	*Length of Treatment*	*Number of Cases*	*Intensity of the Reaction*		
			++	+	+−
By mouth	1 month	2		2	
" "	2 months	3	1	2	
" "	3 "	4	2	2	
" "	5 "	6	3	3	
" "	6 "	10	7	1	2
" "	7 "	4	3	1	
" "	8 "	5	4	1	
" "	9 "	10	7	1	2
" "	10 "	3	2	1	
" "	11 "	3	3		
" "	1 year	24	13	6	5
" "	14 months	2	2		
" "	15 "	2	1	1	
" "	16 "	4	3		1
" "	17 "	1	1		
" "	18 "	7	1	4	2
" "	19 "	4	3	1	
" "	20 "	2	1	1	
" "	2 years	15	8	5	2
" "	2.5 "	3		2	1
" "	3 "	5	1	2	2
" "	4 "	1	1		
By mouth*	7 "	1		1	
By mouth*	10 "	1	1		
By mouth*	12 "	1		1	
Inunctions	2 months	2	2		
"	5 "	1		1	
"	6 "	2	2		
"	1 year	1	1		

* Interrupted treatment during this time. ++ indicates complete inhibition of hemolysis.

Mercury not a Staple Curative Agent

"The table illustrates very well the effect of treatment with mercury upon the Wassermann reaction, as it occurs in the usual routine of serological work in a Wassermann laboratory. It shows that continued treatment with the drug for long periods of time has but little effect upon the reaction in the majority of instances and that interrupted treatment continued for many years does not produce a negative reaction in many cases.

"It should not be thought, however, from the data given here, that the Wassermann reaction never becomes negative after treatment with mercury, for in a considerable proportion of cases it does, and the writer has observed many cases in which a negative Wassermann reaction was obtained after from one to two years' proper treatment with this drug, but it has been his experience that **most cases becoming negative after mercurial treatnent relapse in the course of months or a year or two.** While he would not go so far as to state that the Wassermann test never becomes permanently negative after treatment with mercury, it has been his experience that it is **only in very rare instances that a permanently negative result is obtained from treatment with this drug alone,** no matter how it is administered or in what dosage.

"In fact, it has been proved in rabbits experimentally infected with syphilis, that before the animals can be rendered sterile as regards treponema pallidum so much mercury has to be administered as to cause either the death of the animal or very serious pathological lesions due to the drug. In the writer's rather large experience he has never personally followed a case treated with mercury alone, in which the Wassermann test was positive before treatment, that became permanently negative, although many cases have lost the positive reaction for a while but have invariably become positive again upon the cessation of treatment. However, that mercury does cure syphilis in some instances, is proved by the fact that individuals are encountered who undoubtedly had the disease but who have been without symptoms for many years and who give a negative Wassermann reaction whenever tested.

"If the patient's blood serum be carefully titrated after the administration of either salvarsan or mercury, it will be found that in almost every instance the Wassermann reaction is influenced to some extent, although it may never become negative. Thus, many cases showing a two plus reaction, or absolute inhibition of hemolysis, with quantities of blood serum as small as 0.02 c. c. will become negative for this amount of serum, although giving a positive reaction with the usual quantity of serum used in the routine tests; *i. e.*, 0.1 c. c. By titrating the inhibitory strength of each patient's serum it will be found that, although the Wassermann test may apparently be uninfluenced when the diagnostic amount of serum is used, that is, 0.1 c. c., some diminution in the strength of the reaction will be observed in amounts less than 0.1 c. c. In using the Wassermann test as a control of treatment the titration of the patient's serum is of great importance, as will be noted.

"Not only will treatment with salvarsan or mercury markedly influence the strength of the reaction but if treatment is commenced early in the primary stage of the disease it will sometimes prevent the development of a positive reaction, although clinical symptoms may occur."

CHAPTER XII

THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

It is unnecessary in a book, enabling the general practitioner to formulate a technic for the ordinary uses of salvarsan and neosalvarsan, to discuss in elaborate detail the treatment of syphilis of the central nervous system. For purposes of information, however, the method of utilizing salvarsan in the direct treatment of interstitial and parenchymatous lues are herein briefly set forth.

Swift-Ellis Method

This method was brought to the attention of the medical profession by Drs. Homer F. Swift and Arthur M. W. Ellis, of New York, in 1912 (*N. Y. Med. Jour.*, July 13, 1912) and, with some modifications, is still in use.

The original technic was to withdraw the blood into large tubes by means of a MacRae venous puncture needle, after intravenous injections of salvarsan or neosalvarsan, to separate the serum and, on the following day to dilute it to 40 per cent with normal saline and to heat it at 56° C. for thirty minutes. By lumbar puncture, 15 c. c. of spinal fluid was withdrawn, and then 30 c. c. of the diluted serum was warmed to body temperature and was slowly injected into the subarachnoid space. The foot of the bed was raised for one-half hour after treatment. Drs. Swift and Ellis found that there might be a slight rise in temperature after the injection, and that in tabetics there were often lightning pains in the legs. The reaction usually passed off by the following day and the patients were able to be up and around the hospital.

In concluding their original article, they observed that the best results could probably be obtained from the intravenous treatment with salvarsan or neosalvarsan, combined with in-

traspinous injections of the patient's own serum, possibly with the addition of small amounts of neosalvarsan.

Technic of Subarachnoid Injections

Drs. Swift and Ellis read a paper before the Association of American Physicians, May 7, 1913, in which they set forth the following technic of subarachnoid injections:

"One hour after the intravenous injection of salvarsan 40 c. c. of blood is withdrawn directly into bottle-shaped centrifuge tubes, and allowed to coagulate, after which it is centrifugalized. The following day 12 c. c. of serum is pipetted off and diluted with 18 c. c. of normal saline. This 40 per cent serum [1] is then heated at 56° C. for one-half hour. After lumbar puncture the cerebrospinal fluid is withdrawn until the pressure is reduced to 30 mm. cerebrospinal fluid pressure. The barrel of a 20 c. c. Luer syringe (which has a capacity of about 30 c. c.) is connected to the needle by means of a rubber tube about 40 cm. long. The tubing is then allowed to fill with cerebrospinal fluid so that no air will be injected.

"The serum is then poured into the syringe and allowed to flow slowly into the subarachnoid space by means of gravity. At times it is necessary to insert the plunger of the syringe to inject the last 5 c. c. of fluid. It is important that the larger part of the serum should be injected by gravity and if the rubber tubing is not more than 40 cm. long the pressure cannot be higher than 400 mm. Usually the serum flows in easily under even a lower pressure. By the gravity method the danger of suddenly increasing the intraspinous pressure to the danger point, such as might occur with rapid injection with a syringe, is avoided. Frequently there is a certain amount of pain in the legs, commencing a few hours after the injection. The pain is more often noticed in tabetics than in patients with cerebrospinal syphilis. It can usually be controlled by means of phenacetin and codein. Occasionally morphin is required."

[1] In patients who do not have reactions following the injection of 40 per cent serum, the strength is at times increased to 50 or 60 per cent, or even stronger.

Continued observation demonstrated to their satisfaction that this method had a curative action on the syphilitic process and that, where especially intensive treatment was required, as in rapidly advancing tabes or paresis, or where the disease had resisted other forms of treatment, it was especially indicated.

Observations on Types of Response

Dr. Swift's last paper read before the College of Physicians, Philadelphia, February 7, 1917, is on his Observations on Types of Response in the Treatment of Syphilis of the Central Nervous System (*Amer. Jour. Syph.*, Vol. 1, No. 3, July, 1917). He classifies the various types under the following main headings:

1. Vascular.—The essential lesion is an endarteritis, and the nervous lesion is due to disturbed circulation.

2. Exudative.—The most marked lesion is cellular thickening of the supporting membranes or perivascular spaces, with gumma formation and subsequent mechanical injury to cortex, tracts, and intradural portions of nerves.

3. Parenchymatous.—The striking picture is tract or cortical degeneration, but in which the essential lesion is probably a chronic meningitis and perivasculitis. At least this appears to be true of the various tabetic manifestations. In paresis a true inflammation of the cortex seems to exist. This peculiarity in the paretic process probably explains the intractability of this condition to treatment.

The various factors considered in classifying the cases have been found by Dr. Swift to be: time since infection; the clinical picture; the laboratory findings; and the response to treatment. He recognizes these groups:

1. Early Meningitis.

(a) Cases which respond readily to the general administration of salvarsan and mercury.

(b) Cases which respond more slowly to salvarsan intravenously, and tend to relapse when salvarsan is discontinued, or mercury is substituted.

(c) Cases which do not clear up under most intensive general treatment, but which respond satisfactorily to intraspinal treatment.

2. Later Forms of Central Nervous Syphilis of the Exudative Type.

The abnormal elements in the cerebrospinal fluid usually disappear rapidly under general administration of iodides, mercury and salvarsan.

3. Tabes Dorsalis.

(a) Cases which show a rapid response to general treatment.

(b) Cases which show no improvement or very slow improvement under general treatment.

(c) Cases which show a satisfactory response to intraspinal treatment alone.

(d) Cases which have responded slowly to general treatment, but which respond more rapidly when intraspinal injections of "autosalvarsanized serum" are given.

(e) Cases which relapse when treatment is discontinued.

(f) Cases which continue to improve when treatment is discontinued.

4. Paralytica Dementia.

(a) Cases with marked improvement in both clinical signs and the condition of the cerebrospinal fluid.

(b) Cases with marked clinical improvement but no change in the cerebrospinal fluid.

(c) Cases with progressive downward clinical course and stationary condition of the cerebrospinal fluid.

5. Patients Clinically not Paralytica Dementia in whom the Cerebro-spinal Fluid shows a Paretic Type of Gold Curve.

(a) Cases which respond rapidly to combined intravenous and intraspinal treatment.

(b) Cases which respond more slowly and show a decided tendency for the abnormal elements to recur when treatment is discontinued.

Summarized Conclusions

The conclusions reached, following a very comprehensive study of the conditions, are:

"Before undertaking the treatment of a patient with any form of cerebrospinal syphilis, it is important to determine what symptoms are due to inflammation or exudation and what are due to degeneration of tracts or cortex. It is also advisable to determine the intensity of the irritative condition as indicated by the cerebrospinal fluid. In general the lesions due to inflammation or exudation are much improved or eliminated by the general treatment of the patient. Those due to degeneration are little, if any, affected.

"Treatment should be directed not only towards the elimination of symptoms, but towards the elimination of the underlying process, namely, syphilis. In most patients with early meningitis and in those with what was formerly termed tertiary syphilis of the central nervous system, the symptoms due to exudation respond in a satisfactory manner to the general administration of salvarsan, mercury, and potassium iodid.

"Occasionally, a case is met in which intraspinal treatment seems to be necessary in order to eradicate completely the central nervous lesions. Likewise in tabes dorsalis, many cases respond satisfactorily to the general administration of salvarsan and mercury. On the other hand, in a considerable number of tabetics, the addition of intraspinal injections of serum to intravenous treatment with salvarsan seems to hasten the elimination of abnormal elements in the cerebrospinal fluid and leads to a permanent arrest of the degeneration.

"It is advisable to continue the treatment of patients suffering from cerebrospinal syphilis or tabes dorsalis until the cerebrospinal fluid is normal and remains so. A possible exception may be made in reference to excess globulin, for an increased globulin is not infrequently found years after all other abnormal elements have disappeared from the fluid.

"In paralytica dementia, while much benefit may be expected in increasing the number and length of remissions, the ultimate

hope for recovery is slight. When a paretic type of gold curve is found in the fluid of patients in whom the clinical diagnosis of paresis is not justified, the most intensive form of treatment should be instituted from the beginning. It is probable that the finding of this paretic type of gold curve often helps us to make a diagnosis of paresis before clinical symptoms of the disease are present. This early diagnosis with consequent early treatment may be of extreme importance in preventing the development of the outspoken condition.

"Finally, treatment must be individualized, given in courses, and the condition of the fluid determined at the end of each course and at the beginning of the subsequent course. In this way, the indication for kind of treatment, as well as the manner of response, is much more certainly determined than if we depend on clinical symptoms and objective findings alone."

Dr. Ogilvie's Modification

Dr. Hanson S. Ogilvie of New York, believes it necessary to eliminate the uncertain salvarsan content of the Swift-Ellis serum by preparing in vitro a serum of definitely known therapeutic value. His technic is as follows (*Amer. Jour. Syph.*, Vol. I, No. 3, July, 1917):

"Ten cubic centimeters of *clear* human serum are obtained either by centrifuging a tube of freshly drawn blood at approximately 3000 revolutions for from ten to fifteen minutes, or permitting a clot to form by letting it stand overnight. (Originally 15 c. c. was recommended, but it has since been found that the smaller amount is sufficient, and productive of equally as good results.) It is not essential that an autogenous serum be employed.

"Sera taken indiscriminately from patients can be used, and where a large number of patients are to be treated the sera can be pooled and divided into amounts of 10 c. c. each. Care should be taken to free the serum absolutely from fibrin and cellular elements, and to this end it is sometimes necessary to centrifuge a second time. Under no circumstances should a serum be used that contains hemolized red blood cells. The test tube containing

the serum is then placed in a water bath at body temperature until the salvarsan is ready to be added.

"*In preparing the salvarsan solution the greatest care must be exercised in alkalinizing it.* The sodium hydroxid solution must be fresh (preferably not more than four or five days old), and only a sufficient amount added to *very faintly* alkalinize the salvarsan solution. The salvarsan solution will be more readily and accurately alkalinized if the sodium hydroxid is added while the former is about body temperature.

"A very hot salvarsan solution requires more sodium hydroxid to faintly alkalinize it, but when it is cooled down the degree of alkalinity is apparently markedly increased, and a serum charged with such a solution invariably produces a reaction (usually root pain) when given intraspinally. The salvarsan solution should be prepared so that each cubic centimeter contains one milligram of the drug. While at first thought of minor importance, this part of the technic should be carefully considered.

"Unless one is familiar with laboratory work to some extent he is liable to miscalculate his dilution strengths and give more of the drug than is intended. With a 1 c. c. pipette, graduated into tenths or twentieths, the exact amount of salvarsan desired for the case under treatment is added to the ten cubic centimeters of serum, care being taken that the two solutions are at the same temperature (preferably 37.5° C.). The serum should then be gently agitated to insure thorough mixing. It is now placed in a water bath thermostat at 37.5° C. for forty-five minutes. From this it is placed in a thermostat at 56.0° C. for thirty minutes, after which it is removed from the water bath and as soon as the temperature is reduced to approximately that of the body, it is ready to be given to the patient."

Suggestions in Intraspinal Treatment

No changes have been made in this technic since 1917. Dr. Ogilvie insists that the serum should be given not later than three hours after it is removed from the last thermostat, and that the treatment is better borne if it be given within an hour of its preparation.

He also states that salvarsan and not neosalvarsan should be employed for intraspinal injection.

In paresis Dr. Ogilvie employs a relatively stronger serum than in other types of neurologic syphilis, but he states that the maximum amount of salvarsan that can be given with safety is one-half of a milligram, and that treatments with this strength should rarely be repeated oftener than every two weeks.

He decries making a lumbar puncture with the patient sitting up, and he warns that after the treatment the patient should be kept on his back without pillows for from five to six hours and in a recumbent position for from thirty-six to forty-eight hours.

He lays particular emphasis on the fact that while intraspinal treatment is of the greatest value in certain types, such as the interstitial (formerly referred to as the cerebrospinal), it can accomplish little more than the intravenous in others, such as the parenchymatous; and, furthermore, that not every case of interstitial syphilis of the central nervous system, where the cord or the cerebrum is involved, requires intraspinal treatment. A relatively small percentage of cases apparently respond quite as well to intravenous treatment with mercury intramuscularly.

Dr. Ogilvie is further of the opinion that physicians generally have the impression that every one of these cases should be treated intraspinally, but he says that a careful study of the cerebrospinal fluid findings and the clinical picture presented should decide which course is the proper one to pursue.

A Persistent Positive Means a Spirochetal Focus

The physician has to bear in mind that a persistent positive Wassermann always indicates a spirochetal focus in the body. These may be in a quasi-harmless symbiosis in an unimportant tissue of the body and, consequently, it is unnecessary to subject the patient to continuous courses of treatment. On the other hand, however, the offending focus may be in the nervous or the vascular systems and, therefore, a very thorough examination is demanded. The lumbar puncture and the cytologic examination of the cerebrospinal fluid, and use of the globulin test and the colloidal gold test and every other diagnostic test are absolutely

demanded. Syphilologists agree that even in the absence of signs pointing directly to invasion of the nervous system in the face of a Wassermann which continues persistently positive, the physician is justified in doing a lumbar puncture.

Importance of Intraspinal Treatment

Dr. John A. Fordyce of Columbia University, the leading authority on syphilis in the United States, in a paper entitled "Intra-spinal Therapy in Neurosyphilis" (*Am. Jour. Syphl.*, Vol. III, No. 2, July, 1919) says that until conclusion by clinical study, serology and autopsy findings leads to the belief that foci are established in the various tissues, it may require years to modify or destroy functional capacity. He believes that **a complete cure is the exception rather than the rule unless treatment is begun in the early months of the infection.** An aortitis or aortic insufficiency is not the result of a sudden invasion by spirochetes many years after the primary sore, but the effect of a slow tissue reaction due to the implantation of the organisms in the florid stage of the disease. In the central nervous system the spirochetal attacks may cause marked subjective or objective symptoms and signs like headache, delirium or paralysis. On the other hand, an individual so infected may remain free from all symptoms for years until some important center or tract is compromised.

Dr. Fordyce believes that the spirochete may be deposited in the cerebral cortex during the period of generalization of the organisms, and remain hidden away in the deeper parts of the brain and, only in after years, will they produce a disturbance of function. In certain cases they may temporarily stimulate the intellectual powers and lead to achievements of more than normal brilliancy.

The progress of the infection in the central nervous system may be modified or delayed by therapeutic agents, but it is seldom cured. The modified or delayed infection is latent for a time and then relapses. This condition may continue for years before it finally terminates in irreparable damage.

Necessity of Locating the Focus of Infection

Dr. Fordyce emphasizes the necessity of locating the focus of infection and his statistics show that a larger percentage of deaths are due to cardiovascular disease of syphilitic origin than to any other phase of the disease. Therefore, when a persistent positive serum reaction is present, he advises a careful examination of the heart and aorta.

A positive Wassermann reaction which remains uninfluenced by intensive treatment for years, or which returns after a discontinuance of treatment, is often caused by neurosyphilis without any or with very few objective signs. **The blood reaction may become negative after treatment but it will be re-infected by the spinal fluid.** Dr. Fordyce lays especial emphasis on this fact.

During the past five years he has had a very large experience with intraspinal treatment, and he finds that a serum properly prepared and diluted with from 30 to 40 c. c. of spinal fluid before introduction into the spinal canal may be employed without danger in a vast majority of patients in whom indications are present for its use.

The Fordyce Technic

"The patient is given an intravenous injection of salvarsan and approximately one-half hour later 50 c. c. of blood are withdrawn from an arm vein. This is permitted to clot over night in the refrigerator. The next morning it is centrifugalized and the serum pipetted into a sterile tube. After a second centrifugalization to insure removal of all red blood cells the clear serum is pipetted into another tube. To this is added the desired amount of salvarsan, namely: from $^1/_{10}$ to ¼, $^1/_3$ or in certain cases of paresis ½ mg. This mixture is then inactivated at 55 to 57° C. for ½ hour.

"To arrive at the proper dosage for intraspinal therapy we make a dilution of salvarsan of which 30 c. c. represents 0.1 gram of the drug; 10 c. c. is then further diluted with 0.5 per cent saline solution to 35 c. c. of which 1 c. c. equals 1 mg. of salvarsan. In the administration of the medicated serum a lumbar puncture

is made and about 10 to 20 c. c. of fluid withdrawn. A small gravity tube with a capacity of about 40 c. c. is then attached to the needle and the fluid allowed to flow in until it holds about 30 c. c. To this is slowly added the serum and the mixture is permitted to flow back into the canal."

Types which call for Intraspinal Treatment

Dr. Fordyce makes his position clear regarding the indications for intraspinal therapy in that he believes the method in question is of value "in certain types of neurosyphilis which fail to respond to treatment by other channels and in which the spinal fluid reveals an active syphilitic lesion. If a patient after intensive treatment with arsphenamine, mercury and potassium iodid shows little or no improvement in his symptoms, blood or fluid reactions, some other method of therapeutic attack would be clearly indicated."

He finds that intraspinal treatment has been followed by persistent negative phases and clinical improvement or cure and, he is therefore, much more convinced of its value. Since adding salvarsanized serum to 30 or 40 c. c. of withdrawn fluid and permitting the mixture to slowly return by gravity his results have been more rapid and striking.

Dr. Fordyce has a list of seventy-five cases of various neurosyphilitic types in which the findings are negative and many of them have been persistently so for periods of from one to three years. He observes that activation of latent foci or lesions in the central nervous system may follow the administration of mercury or salvarsan and cause an acute encephalitis and death. These so-called Herxheimer reactions as a rule subside and are followed frequently by clinical improvement. It is not always possible to foresee them but they can usually be prevented by a careful preliminary use of mercury and salvarsan in moderate doses before the use of salvarsanized serum intraspinally.

Intraspinal Treatment in Preserving Vision

Emphasizing the necessity of systematic eye examinations in all cases of lues, Dr. Fordyce expresses the opinion that every

case of optic atrophy, whether primary or part of a tabetic or paretic syndrome, **demands an examination of the spinal fluid** at the earliest possible moment. In case the spinal fluid shows primary or associated meningitis, with other positive phases of syphilis, a method of treatment should be begun which offers hope of arresting the destructive process. His experience is that but little can be expected from mercury, potassium iodid or salvarsan intravenously, and he believes that **intraspinal treatment is indicated in optic atrophy** where the fluid shows a meningitis with the positive phases of syphilis.

Persistent intraspinal treatment when indicated by the fluid findings **can arrest the progress of many cases and preserve the remaining vision.** Salvarsanized serum directly introduced into the lumbar subarachnoid space diffuses itself more slowly and accomplishes less than when diluted outside the body with a large quantity of fluid.

Dr. Fordyce feels that too little time has elapsed since beginning the examination of the spinal fluid in secondary syphilis to enable him to speak with certainty as to the type of early neurosyphilis which may develop paresis. He has, however, spinal fluid tests which indicate the probable site of the syphilitic infection of the central nervous system and a large number showing to what degree these reactions resist therapeutic attacks which influence the more superficial types of neurosyphilis. He regards as of favorable prognostic import a spinal fluid which shows a positive Wassermann reaction in the lower dilutions with a luetic gold sol curve, that is so far as regards the positive development of paresis. A persistent reaction in the high dilutions, however, with a paretic curve is of graver significance. When little or no impression can be made on the Wassermann in the spinal fluid by persistent intraspinal treatment, the probable development of paresis must always be kept in mind.

Encouraging Results in Pre-paresis

He observes that the results obtained by the intraspinal treatment in pre-paresis when sufficiently prolonged at times are so encouraging that he feels justified in carrying it out to the limit

of the patient's endurance. He believes that with the careful technic now employed and with the proper preparatory treatment danger to the patient's life or possible damage to the cord or brain has been entirely eliminated. He remarks in this connection that such treatment by the inexperienced without laboratory facilities and proper serological control will certainly fail.

Summary of Dr. Fordyce's Conclusions

"Results following the treatment of syphilis are largely dependent on the age of the infection. For this reason the importance of early diagnosis and energetic treatment have been emphasized.

"In early syphilis the spirochetes are numerous, widely disseminated and cause little or no tissue destruction, organisms accessible to the specific drugs are destroyed and in favorable cases cures are obtained. In a large percentage of cases, however, the treatment is not carried out in an intensive fashion and as a result the organisms persist in the viscera, cardio-vascular or nervous system and slowly cause tissue reactions and final degeneration.

"A serological cure in cases of syphilis in the late secondary stage and following this is difficult to obtain and requires expert knowledge in the use of our therapeutic agents.

"When the central nervous system is invaded the problem is complicated by the highly organized nature of the tissues, the results of secondary degenerations and the inaccessibility of the spirochete in certain types of neurosyphilis. In the majority of cases a strain of spirochete invades the cerebrospinal axis before or during the treatment by drugs by the usual channels and fails to respond to continuous administration of antisphilitic agents given in this way. The progress of the infection may be delayed by drugs assisted by the defensive forces of the body. It is seldom cured. Clinical symptoms are modified or disappear for a time but usually return unless the serology of the spinal fluid and blood becomes negative for a definite period.

"The control of the pathological changes in the brain and cord

is only possible by repeated examinations of the spinal fluid. We have no definite data as to the number of cases of neurosyphilis cured by the older methods of treatment. Frequent relapses and eventual termination in degenerations of the majority of cases so treated lead to the belief that few were cured. The need, therefore, is for a more direct method of attacking spirochete in the central nervous system.

Intensive Treatment Indicated

"The intensive use of salvarsan intravenously combined with mercury and potassium iodid cures a definite number of cases. All methods of treatment fail in certain types of neurosyphilis because of the inability to reach the organisms in inaccessible localities and because of secondary degenerations of tissue which cannot be restored. Intra-spinal treatment is successful in certain types which fail to respond to other methods or which become stationary after a definite clinical and serological improvement.

"Success or failure in the use of intraspinal therapy depends on the technic employed and the persistence of the physician in carrying it out. Above all it depends on the cyto-biological indications which are present in the spinal fluid for initiating or persisting in this mode of therapy.

"The cytology is usually the first phase to be influenced in persistent infections. In some cases treatment must be continued for from one to two years before a definite impression is made on the globulin content or the Wassermann reaction. Modification in the intensity of the globulin reaction is usually followed by a weakening in the strength of the Wassermann and by a change in the gold sol reaction. Rapid changes in the Wassermann reaction where strongly positive in the high dilutions, in my experience, do not occur except in cases of early syphilitic meningitis. In old cases of neurosyphilis a gradual diminution in the intensity of the Wassermann reaction is of good prognostic import and, when it finally becomes negative, cases I have examined after one, two and three years have shown no return of any of the previous phases."

Intravenous rather than Intraspinal Medication

Another school favors the treatment of syphilis of the nervous system by intensive intravenous rather than intraspinal medication. Dr. Bernard Sachs of Mt. Sinai Hospital, New York, is the leader of this school. He believes that by the intravenous method no lives are lost, no unnecessary paralyses result from treatment and far less harm will be done than if the intraspinal method were generally adopted. He points out (*Arch. Neur. and Psych.*, Vol. 1, pp. 277–284, March, 1919) that the early and persistent use of arsphenamine intravenously administered makes the entire course of the disease far less progressive than formerly. He thinks it no exaggeration to state that in innumerable cases he has been able to check the progress of the disease. He says "there is a vast difference between the acute infectious disorders and the more chronic syphilitic disease dependent on the difference in the manner of invasion in the toxic products formed and in the final habitat of the respective micro-organisms.

"In general paresis and in tabes the chief lesions are within the substance of the brain or of the cord far removed from actual contact with the cerebrospinal fluid. It is for that reason almost impossible to bring the spirocheticidal remedy into immediate contact with the foci of disease unless these remedies can be introduced through the blood streams. It is only in the earliest stages of tabes dorsalis that the disease, as we have long since known, involves the meninges and the spinal ganglia; later on it sets up marked degenerative changes in the spinal tissue, and these secondary changes are entirely beyond the reach of the cerebrospinal fluid and its contents. In the remaining meningo-encephalitic and meningo-myelitic processes of specific origin, more or less exudative in character, we would suppose that spirocheticidal substances introduced in the cerebrospinal fluid might have an active therapeutic effect if such substances could course freely in the cerebrospinal fluid and if it could be shown that they were retained in this fluid for any satisfactory period of time.

"Four years ago, with the assistance of Professor Benedict,

we succeeded in showing that salvarsan introduced in the usual quantities into the blood current appeared in the cerebrospinal fluid in appreciable quantities. In this way we refuted the doctrine of the impermeability of the choroid plexus and that salvarsan introduced intravenously could not be expected to exert any influence over the cerebral and spinal tissues. The question, therefore, narrowed itself practically to this: Whether or not as much spirocheticidal substances—for example, arsphenamine—reached the cerebrospinal canal in intravenous treatment, as it was safe to introduce directly into the cerebrospinal fluid by lumba puncture."

A Direct Versus a Round-about Route

Dr. Sachs sets forth the fact that when a metallic substance, like arsphenamine, is introduced into the spinal canal it is rapidly absorbed into the venous system and asks, if this be true, "why not use the venous system at once for the conveyance of this metallic substance rather than the round-about route via the cerebrospinal canal."

He also shows that British authors, among them Halliburton, have abandoned the use of arsphenamine in locomotor ataxia and other late syphilitic affections through the cerebrospinal fluid, because they claim it is fatal both to the syphilitic organism and to the patient.

In his own service at Mt. Sinai, Dr. Sachs observes that he has obtained the most satisfactory results "from intravenous injections administered on alternate days for a period of three to four weeks according to the symptoms presented by the patient, and then allowing a period of complete rest or giving weekly or semi-weekly injections of salicylate of mercury for a period of four to six weeks and then again starting in with the same course of arsphenamine injections. Some of the patients have received as many as forty or fifty intravenous injections within a period of a year or eighteen months. There may be a few men who could with impunity give the same number of intraspinal injections, but the patient will certainly be none the better for

them and even the most skillful of the intraspinal injectionists have had disagreeable experience to record."

Intravenous Method Unsurpassed

Dr. Sachs is emphatic in his statement that no other specific medication has ever been as satisfactory as the intravenous use of arsphenamine. Where there is good reason to suspect that the symptoms of nervous diseases are due to the specific poison, the antisyphilitic medication should be begun as early as possible and persisted in as long as possible.

"In the cases of intense headaches, probably meningeal, in some of the earliest forms of specific optic neuritis, in the large number of cases of cerebrospinal syphilis with actual nerve palsies with moderate paralytic symptoms, with incomplete vesical disturbance; in the victims of vascular disease, in arteritis luetica, and above all, in a rather important group of syphilitic epilepsies, intensive intravenous treatment leads not infrequently to a cure and very often to a marked improvement in all the symptoms. But in this group of cases it is easy for us to realize that the morbid process is largely confined to the meninges and to the surface of the cortical or spinal tissue, but the spirochete can no doubt be reached through vascular channels.

"A group of purely spastic palsies with very slight sensory changes, with little or no vesical disturbance, with much more rigidity than paralysis, the group which Erb so well described and which is long since recognized as a purely degenerative group, yields least to intravenous or to any other forms of antisyphilitic medication. The question of the effective treatment is most in doubt when we come to consider the results in locomotor ataxia. The tabetic pains, the crises, the bladder symptoms, and the sexual impotence, may be relieved by antisyphilitic medication as we have known them to be relieved by prolonged periods of rest, by hydro-therapeutic procedures, by mercurial injections, by almost any other method of treatment that has from time to time been advocated for the treatment of tabes dorsalis."

A Study of Four Hundred Cases

Dr. Sachs gives these facts to show why he has pinned his faith to the intravenous use of salvarsan, or neosalvarsan, and why he has rejected the more dangerous intraspinal method of treatment. He refers to an article by his associates, Drs. Kaliski and Strauss, on "Syphilis of the Nervous System" (*Am. Jour. Syph.*, p. 609, October, 1918), in which a careful critical study of over four hundred cases from Sachs service is considered.

In the treatment of early cerebrospinal syphilis, early tabes dorsalis, early cases of Erb's spastic paraplegia and those early cases of syphilis without nervous symptoms at all or with very persistent cephalalgia presenting biological changes in the spinal fluid, they utilize salvarsan or one of its safe substitutes. The drug is given intravenously every day or every other day in doses of 0.2 to 0.3 gram until a total of from 1 gram to 1.2 grams is given within a period of seven days. This intensive treatment can be safely kept up, they advise us, for a period of from four to eight weeks, nor do they consider it necessary to give the drug more than three times a week for more than from four to six weeks. On alternate days, deep intramuscular injections of bichloride of mercury in doses of $^1/_5$ grain upwards every second or third day, or salicylate of mercury, 1 to 2 grains every fourth or fifth day are given.

In lesions of the gummatous type the authors advise the use of the iodides, 30 to 60 grains three times a day, in addition to the salvarsan treatment.

Where the symptoms are not so urgent, as in the more chronic cases of cerebrospinal lues and tabes, they give from 0.8 gram to 1.0 gram of salvarsan each week with or without injections or inunctions of mercury.

In the less urgent cases the intravenous injections are kept up from six to eight weeks. At the end of this time, there is a rest period of from one to two months.

Drs. Kaliski and Strauss make another group of more chronic cases, especially those with the more persistent type of cerebrospinal lues and tabes, with persistent positive reactions in the

blood and spinal fluid, and with mild subjective symptoms. They administer to patients in this group salvarsan from 0.3 to 0.4 gram twice a week where feasible, or possibly every fifth or sixth day for a period of from six to eight weeks, accompanied by salicylate of mercury injections 1 to 2 grains every fifth day for two months, or they utilize inunctions.

In the first group, after the disappearance of the distinctive symptoms, they do not believe it necessary to maintain the very intensive salvarsan therapy for the full period of eight weeks, but treat the patients as they do those in the second group if improvement has been satisfactory, and in these cases they give salvarsan from not more than twice a week to three times a fortnight.

After the resumption of treatment, following the rest period, the next course, they say, must be governed entirely by the nature of the symptoms. If there is pain, paresthesias, crises, and bladder and rectal disturbances, they advise a second course of salvarsan intravenously followed by mercury, but they do not administer salvarsan oftener than once a week in doses of 0.4 to 0.5 gram for a course of eight injections. They remark that if they use neosalvarsan a third larger dose in every instance is given. For the purpose of determination of the condition of the spinal fluid in cases treated only intravenously a lumbar puncture is performed once or preferably twice during each course of treatment.

Persistence in Treatment Necessary

Drs. Kaliski and Strauss emphasize the necessity of the persistence in treatment after the initial few months of intensive therapy for from one to two years, with increasingly greater intervals between treatments. They suggest that after the cessation of active symptoms the patient should report from once to twice a year for observation and further treatment, because many of these persons not only have a lesion of the nervous system but a syphilitic aortitis, myocarditis, endo-neuritis, or some other condition which needs watching.

They specify a third group in which they place cases of more

advanced tabes dorsalis, late cerebrospinal lues, optic nerve atrophies, spastic paraplegias, and chronic syphilitic epilepsy. Destructive lesions involving one or more extremities and pain and crises may be the predominating factors in these conditions, and they observe that they can frequently bring about the gradual abolition of pain and the occasional disappearance of the crises. Optic atrophy cannot be cured but occasionally can be arrested, although they are not optimistic about this condition. Their experience has shown that intravenous therapy aids the ataxia of these cases, particularly when used with re-educational and other local measures. In this group they administer salvarsan every two weeks or, on occasion, every week, in doses of 0.4 to 0.5 gram for from two to three months and follow it by inunctions or injections of mercury. If ataxia is marked, mercury by injection must be administered with care and for that reason they prefer the inunctions.

In discussion of the treatment of general paresis, Drs. Kaliski and Strauss are of the opinion that so far as the use of salvarsan is concerned, they are not yet in position to make a definite statement on account of the lack of sufficient data and the brief period of observation since salvarsan was introduced. They have had a variety of results in the treatment of this condition, the prognosis of which is uniformly bad, and while there were some patients who after treatment have had no relapse for more than two years, they have had others in whom the treatment was ineffective in bringing about much improvement. Their method of treatment is that indicated in the caring for the conditions in group 1.

Syphilis shows few Contraindications to Arsphenamine and Mercury

They state there are few contraindications to the use of arsphenamine and mercury in the treatment of syphilis. Optic neuritis is not a contraindication, nor is optic atrophy necessarily one, although in the latter condition it must be used with great care. Cardiovascular conditions, particularly when accompanied by high blood pressure and renal involvement require

great care in dosage and frequency of treatment. They rema that the prime determining factor concerning the possibility arsphenamine treatment is the integrity of the kidneys and th recommend very careful urinary examinations. They say th "it is not always necessary to avoid salvarsan therapy becau of the presence of a mild nephritis, but where treatment is giv the dosage should be conservative and the frequency of the a ministration of the drug such as to permit elimination of mo of the arsenic before the second injection is given." They do n give salvarsan more than once in two weeks in these condition

They also note that certain persons have a hypersensitivene to arsphenamine, a phenomenon which usually makes itse manifest after two or three injections. They think the patie has been sensitized by the previous injections, and that the r actions are due to the toxic action of the drug on the vasomot system. They point out as the first signs of the anaphylactoi reaction slight dilatation of the vessels of the conjunctivæ or ski feeling of warmth in the face, tickling in the throat, desire t cough, slight abdominal rumblings or cramps, feeling of fullne in the head, or difficulty in breathing deeply. They advocate th suspension of the injection without the withdrawal of the needl If the symptoms are progressive, they believe in discontinuir the injection but, if they rapidly pass, they advise the injectic of a few more c. c. in solution and finally if no untoward resul follow, the injection of the entire amount. At the time of sul sequent injections they recommend giving these patients 10 15 minims of a 1:1000 solution of adrenalin subcutaneously 1/100 grain of atropin sulphate fifteen minutes before the a sphenamine injection.

Intravenous First, Intraspinal Later

Dr. Richard W. Harvey of the University of California (*An Jour. Syph.*, p. 785, 1918) in a study of cases which have com under his care at the University Hospital, San Francisco, b lieves that intravenous arsenic preparations are to be employe first in all cases of nervous system lues, accompanied by intr muscular injections of mercury, either the benzoate or salicylat

or, if the patient is in the hospital, by daily inunctions. Intraspinal treatment should be given only after the conservative treatment has been employed and then only for the relief of pain and of crises in tabes and cerebrospinal lues.

Intra-Arterial Injection of Neosalvarsan in Cerebrospinal Syphilis

Dr. David A. Sinclair of New York while of the belief that salvarsan is the most powerful spirocheticide known, feels that its beneficial action in the more serious affections of the cerebrospinal system has not been demonstrated. (*Med. Times*, Vol. XLV, No. 1 and No. 4, pp. 18–89, 1917.) His belief is based on the difficulty of bringing the spirochetes in the perivascular tissues of the brain and spinal cord into close contact with the arsphenamine introduced by ordinary methods.

A careful study of the anatomy of the brain and the arrangement of the blood supply, he says, shows this: the common carotid artery divides into the internal and external carotids. The internal ascends directly to the brain and gives off no branches until it enters the skull. With its fellow of the opposite side and the two vertebral arteries, the circle of Willis is formed through the anterior and posterior communicating arteries. Through this media the brain receives its blood supply. The choroid artery, a branch of the internal carotid, supplies the choroid plexus of the brain, which plexus secretes the cerebrospinal fluid.

Dr. Sinclair's contention is that the injection of neosalvarsan into the internal carotid artery is at once distributed to the brain and at the same time directly feeds the secretory apparatus of the cerebrospinal fluid through the choroid artery.

The articles quoted from the *Medical Times* give the history of a case in which Dr. Sinclair, after some animal experimentation, carried out his belief by injecting five and one-half decigrams of neosalvarsan into the internal carotid artery in a patient suffering from cerebrospinal syphilis. This man had previously been given intravenous injections of neosalvarsan on

four different occasions without improvement of his mental condition, which for three years previous had caused him to act in an extraordinary manner. Under ether anesthesia, Dr. Sinclair opened the tissues of the neck in the left carotid line and separated the internal carotid artery from the jugular vein by passing a grooved director underneath it. A small hypodermic needle was introduced into the lumen of the artery, the syringe attached to the needle, and the neosalvarsan injected. The wound was closed by chromicized catgut and silkworm gut sutures, a compress placed over the line of incision and all held in place by a bandage. The man's condition improved to a very considerable extent. Five weeks later the operation was repeated and nine decigrams of neosalvarsan in 10 c. c. of distilled water were infused into the right internal carotid artery by the same procedure. Twenty-seven days thereafter nine decigrams of neosalvarsan in 10 c. c. of water were given in the left carotid artery. After that there was marked improvement in the man's mental and physical condition.

Dr. Sinclair is of the belief that therapeutic medication through the arterial system offers many opportunities. As an example, he mentions a rebellious syphilis of the extremities. He believes that the brachial or femoral arteries could be utilized as direct carriers of therapeutic agents and thus the consequent dilution which must occur when the intravenous route is used would be avoided.

Intracranial Salvarsan Injection

The intracranial method of the introduction of salvarsan is a favorite with some practitioners. The injection is either intraventricular or subdural.

After four years of this form of treatment, Drs. H. A. Cotton and W. W. Stevenson of the New Jersey State Hospital, Trenton, report (*Jour. Ment. & Nerv. Dis.*, 1918) that the **intracranial method is the most efficacious mode of treatment of paresis,** and should be the method of preference, while the **intraspinal method is the most efficient one for the treatment of tabes and luetic meningitis.** They express the belief that salvarsan is the best

drug for the treatment of cerebrospinal syphilis and is preferable to the substitutes. They urge that the disease should be diagnosed in the pre-paretic stage, or as soon as the symptoms are present, and that there should be a frequent examination of the spinal fluid in every case of syphilis after all symptoms of the acute stage are lost, especially if the Wassermann remains positive after sufficient treatment has been given.

Arrest and Possible Cure of Paresis

They conclude that **all cases of paresis can be arrested and possibly cured** if the treatment is begun early enough.

Drs. Walker and Haller (*Arch. Int. Med.*, Sept., 1916) after a study of seventy-five cases reach the conclusion that patients with recent syphilitic meningitis and cerebrospinal syphilis may be relieved symptomatically by intravenous injections of salvarsan. The spinal fluid reaction may become negative with 1 c. c. and the cell count may become normal. Long standing cases of cerebrospinal syphilis and tabes are likely to be symptomatically benefited by salvarsan but they think there is little or no change in the spinal fluid findings.

Patients with recent as well as late syphilitic meningitis, cerebrospinal syphilis, tabes, and general paresis are markedly improved following intravenous salvarsan and intraspinal salvarsanized serum, and those who fail to improve under one do improve under the combined treatment.

Permeability of the Meninges to Arsenic in Paresis and Tabes

In patients who have received intravenous injections of salvarsan or neosalvarsan it has been demonstrated that the serum contains more than five times as much arsenic as the clot. Within thirty minutes, about 75 per cent of the salvarsan is fixed in the body cells and 24 hours after the intravenous administration of salvarsan, it is found that arsenic has passed into the spinal fluid.

When serum treatment is used, it is readily observed that a soluble arsenic preparation formed from the body cells is being

administered. This preparation contains the larger amount of the arsenic which remains in the circulatory system. It also suggests the need of drawing the blood during the first thirty minutes after the intravenous administration of the drug when it is to be used as a source of serum containing arsenic.

CHAPTER XIII

THE TREATMENT OF CONGENITAL, MALIGNANT AND VISCERAL SYPHILIS

Congenital Syphilis

Various plans for the treatment of congenital syphilis are in vogue, and most syphilologists have their own methods of procedure.

A logical plan has been devised by Eugene Graetzer and is described (*Urol. & Cut. Rev.*, September, 1916) as a course or a series of courses of neosalvarsan and calomel.

A single course consists either of 12 calomel and 8 neosalvarsan injections, or of six weekly inunctions and eight neosalvarsan injections. The courses occupy approximately a period of three months.

The combined calomel-neosalvarsan course is applied according to the following scheme:

Week	*Treatment*
1	Two calomel injections.
2	1st and 2nd neosalvarsan injections.
3	
4	3rd and 4th calomel injections.
5	3rd and 4th neosalvarsan injections.
6	
7	5th and 6th calomel injections.
8	5th and 6th neosalvarsan injections.
9	
10	7th and 8th calomel injections.
11	7th and 8th neosalvarsan injections.
12	
13	9th and 10th calomel injections.
14	11th and 12th calomel injections.

Following this first course there comes a rest for three months, after which the second course begins in the same way; and, after a second rest for three months, the third course in the same proportions takes place. The combined inunction and neosalvarsan cure is applied as follows:

Week	*Treatment*
1	Inunction course (1 week).
2	1st and 2nd neosalvarsan injections.
3	Inunction course (2 weeks).
4	
5	3rd and 4th neosalvarsan injections.
6	
7	Inunction course (3 weeks).
8	5th and 6th neosalvarsan injections.
9	
10	Inunction course (4 weeks).
11	7th and 8th neosalvarsan injections.
12	
13	Inunction course (5 and 6 weeks).
14	

From the second year on, calomel and inunctions are alternated. In infancy, because of the small surface and the sensitiveness of the skin, it is better to avoid inunctions. Dosage, according to Graetzer, is as follows: 0.001 g. calomel and 0.015 g. neosalvarsan per kilogram of body weight. Of course, the first injection of neosalvarsan is less than given in the scale in order that idiosyncrasies may be ascertained. The author has never observed any.

As a site for injecting the calomel and also for the epifascial injections of neosalvarsan, he recommends the thick musculature of the nates in the upper external quadrant. The calomel injections can also be injected into the upper limb. The neosalvarsan is usually applied intravenously in infants, either into the veins of the skull, the ankle-joint, the jugular, or recently, according to L. Tobler, into the sinus longitudinalis. This last mentioned method proved to be very satisfactory, but it is a hospital procedure which limits its field of usefulness. Only in

exceptional cases should infants receive neosalvarsan injections intramuscularly. The author keeps on hand, 3, 4, 5 per cent solutions of calomel in olive oil. With large children he uses preferably the 40 per cent calomel solution of Zichler.

He says "the dosage of the grey ointment for the inunction course is at the rate of 1.0 grm. of ointment to 10 kg. body weight and should not exceed 4.0 g. A child weighing 20 kg. gets six inunctions of 2 g. per week and on the 7th day is bathed."

Treatment of the Expectant Mother

Many men favor treatment of the expectant mother, if she or her husband be syphilitic, in the hope of preventing a luetic child. This plan consists of intensive treatment with salvarsan or neosalvarsan, mercurial inunctions and the iodides.

Dr. Lisser (*Cal. State Jour. Med.*) believes it to be wiser, if the treatment is begun during the early months of pregnancy, to employ frequent small doses of salvarsan, 0.2 to 0.3 to 0.4 gram, rather than the full dose, although it has been shown that salvarsan does not seem to increase the tendency to abortion or hemorrhage. But the total amount of salvarsan should be at least 1.5 grm., and larger amounts are safer.

Such treatment affects the fetus favorably by its curative action on the mother, and in the early stages especially, by preventing disease of the placenta. Furthermore, Meyer has shown in the case of salvarsan, that whereas a normal, sound placenta does not allow arsenic to permeate, the syphilitic placenta does permit the drug to pass through to the fetus.

Findlay and Robertson (*Glasgow Medical Journal*) record several successful examples of such antenatal therapy. "In no case was the course of the pregnancy interrupted, and the mothers did not seem to suffer much from the treatment. The mothers, as a rule, expressed themselves as feeling better during these than during any of their previous pregnancies."

So far as their experience goes, equally good results were obtained whether treatment was commenced as early as the second month or delayed the seventh month of pregnancy. "This in all probability is to be accounted for by the fact that many

syphilitic infants are infected during parturition, the mischief remaining local in the placenta during the whole course of gestation. It is this uterine localization of the disease which accounts for the absence of clinical manifestations in many of the mothers of syphilitic children. Baisch, Trinchese, and Weber working in Döderlein's clinic, found that in the case of every syphilitic child the placenta, both the fetal and maternal portions, contained spirochetes, and in common with Rietschel are inclined to the opinion that the spirochete always travels to the child from the placenta.

"Most authorities agree that during gestation the spirochete may travel along the umbilical cord and infect the fetus, but this according to Rietschel is less frequent than infection by emboli set free during parturition. It would therefore seem exceedingly likely that in the treatment of pregnant women the salvarsan gets easily at the very vascular placenta and destroys the contagium vivum, thus considerably lessening the risk of embolism from living spirochetes."

Antenatal Treatment Versus no Therapy

It is interesting to compare the statistics of such antenatal therapy with the results of no therapy at all. With no treatment of maternal syphilis at all, the primary mortality of congenital syphilis is enormous. In the first year of life, Leduc estimates it at 71 per cent; Zeissl at 80 per cent; Bunch at 90 per cent; Markus at 90 per cent. Hochsinger claims that 93 per cent. of syphilitic children have disease of the nervous system.

According to Galliot, when mothers are treated before pregnancy, but not during pregnancy, 82 per cent of the resulting children are born dead.

Mercurial treatment of the pregnant mother has the following results to commend it: Of 217 infected pregnant women showing signs of active syphilis during their pregnancy, who were vigorously treated with mercury and iodides during their pregnancy, 25 per cent of the resulting progeny were born alive, of whom 10 per cent showed signs of syphilis. This is at once a striking improvement over no treatment at all.

Of 163 pregnant infected women, without signs of active lues, but having so-called latent lues, who likewise were vigorously treated with mercury and iodides during their pregnancy, 66 per cent living children were born who were well clinically; 14 per cent were born alive but showed signs of congenital lues, and 19 per cent were born dead. Pinard, Champetier de Ribes, and Potocki, by prolonged treatment with mercury and potassium iodid, obtained 76 per cent of the children healthy.

Of 128 women with latent lues, who were treated before and during pregnancy with mercury and iodides, 88 per cent living children, clinically well resulted, the remainder showing signs of syphilis. These statistics are surely a strong argument in favor of the thorough treatment of the disease (Galliot).

Fleeting Character of Mercury

But the effect of mercury unless continued is fleeting. This is illustrated in an astonishing manner by the following case reported by Fournier (Meyer). A syphilitic woman was pregnant eleven times. She had no treatment whatsoever during the first seven pregnancies, and the result was seven dead luetic children. During the eighth and ninth pregnancies, energetic mercurial treatment was given, and the result was two healthy children. No treatment was taken during the tenth pregnancy and again a luetic child was born dead. Treatment during the eleventh pregnancy was successful in bringing forth a healthy child. Fournier concludes: "So powerful yet so fleeting is the effect of mercury that, if it were not immoral, I would like to try the experiment of alternately treating and not treating a syphilitic mother, and alternately bringing into the world healthy and syphilitic children."

Advantages of Salvarsan

When salvarsan was combined with such mercurial therapy, remarkable results were obtained, Sauvage reporting 93 per cent and Bourret and Fabre 100 per cent cures. These latter statistics may be somewhat enthusiastic, for it must be admitted that many cases, showing congenital syphilis after reaching 6 to

20 years of age, showed no specific manifestations whatsoever during the first few years of life. Most of the cases reported were only observed during the first few months or first year of life, and are therefore subject to this reservation. Nevertheless, it would seem that this method of antenatal therapy has much to support it and merits extensive trial.

Dr. Lisser notes that another prophylactic measure suggests itself. Suppose that an apparently healthy child, with negative Wassermann and negative luetin, is born from parents known to have active syphilis. In view of the fact above-mentioned, that luetic stigmata do not develop in certain cases until long after infancy, would it not be prudent to administer small doses of mercury intermittently to such a child during the first few years of life? In reasonable quantities such therapy would not be harmful. It might be beneficial. It is almost impossible to bring facts or statistics in favor of such a procedure, for the unanswerable criticism can always be advanced that the particular child so treated may never have developed syphilis anyway. But when one bears in mind the extraordinary obstinacy of just those cases where the disease makes its appearance late in childhood, it would at least appear to be an error on the side of safety to treat prophylactically infants who are the progeny of parents recently tainted with syphilis.

Old salvarsan, unfortunately, has not the wide application in congenital syphilis that it has in the acquired form, Dr. Lisser goes on to say, not because it is less efficacious, but because of the difficulties of administration. Even in acquired syphilis its intramuscular use has been largely abandoned, the pain resulting from the injection and the necrosis and sloughing that not infrequently supervene are very serious objections; and in children the delicacy of the tissues should absolutely prohibit its use in this way. However, salvarsan can and should be used intravenously whenever there is a vein of sufficient size at the bend of the elbow. It should be well diluted and the consequent large amount of fluid to be injected must be allowed to flow into a vein in a position where the flow can be easily controlled.

The jugular vein has been used and likewise the veins of the

scalp, but whereas these routes are excellent in the case of neosalvarsan where highly concentrated solutions can be used and the operation quickly finished, it is difficult to keep the child quiet enough for a sufficiently long period of time to permit the steady flow of 50 to 100 c. c. as is the case when salvarsan is used. In view of the frequency of these injections it does not seem advisable to anesthetize the child, particularly when other efficacious drugs are available. Salvarsan should only be given intravenously, and only into a vein of the forearm. Its dosage must be regulated according to the age and size of the patient, and the first dose should always be exceedingly small. Even in the adult, there is a growing tendency to use smaller individual doses, especially the initial dose; that is from 0.2 to 0.4 gram instead of 0.6 gram. It is evident that much greater caution is necessary in young children; 0.01 gram to every kilo, or 2¼ lbs., is a safe average. It is probably a safe custom to place such children in a hospital over night. Lisser believes that in the comparatively few cases where salvarsan can be used, the results are highly satisfactory. Just as in acquired lues, mercury should invariably be used in combination with the salvarsan. Neither alone is as reliable as both together.

A Wider Field for Neosalvarsan

Neosalvarsan has a wider field of usefulness in congenital syphilis than in the acquired form, Lisser observes, and for the following reasons: Its use in acquired lues is largely a matter of convenience, and can be entirely displaced and should be displaced by the more powerful effect of old salvarsan. But in inherited lues it is invaluable because of the high concentration in which it may be injected.

It can be employed in two ways: first, intravenously, using the veins of the scalp, as first suggested by Neogarrath in 1911. This is the method of choice in infants up to about two years of age. Simpson and Thatcher in 1913 advocated the use of the external jugular, but, in the technic they describe, an anesthetic is necessary, the vein being cut down upon and a cannula inserted. Such a drastic procedure was justified at the time when

it was thought that one large dose would cure the disease, but since experience has demonstrated the necessity of frequently repeated injections, it would be wiser to use other methods at our disposal. By utilizing the veins of the scalp, neosalvarsan can be given in 3 or 4 c. c. of saline or freshly distilled water in an ordinary Record or Luer syringe, and in a very few minutes. The initial dose should be calculated from 0.015 gram per kilo; that is about 0.05 gram for a new-born infant, gradually increasing in successive doses to 0.2 or even 0.3 gram per injection. This dosage has been used with safety and success. Slight reactions such as vomiting, diarrhea, and occasionally fever will result, but no more so and no more serious than occurs frequently in adults.

Epifascial Method of Injection

Wechselmann's so-called epifascial method of injection is serviceable in those children between the ages of 2 and 7, who have neither veins of the scalp for intravenous neosalvarsan nor veins of the forearm for old salvarsan. Wechselmann employs it in his routine treatment of adults, never giving neosalvarsan intravenously, but only epifascially, and reserving the veins for old salvarsan. The technic requires some practice, but once learned, is really very simple, quick, and convenient.

Mercury is as valuable in the treatment of inherited syphilis as salvarsan. To omit its use would be an error. The official blue ointment may be used. The skin of children will not permit vigorous rubbing nor is it necessary. Inunctions should be given six days out of the week. In very small children and infants bichlorid baths are very satisfactory. Twenty or thirty grains of bichlorid mixed with an equal quantity of ammonium chloride should be used.

Oral medication is not satisfactory for several reasons. Absorption from the intestinal tract is uncertain and if the parent is in charge of the treatment, doses may be given irregularly, and when taken faithfully derangements of the intestinal tract are not uncommon. The gray powder, mercury with chalk, in doses of ¼–½ gr., or calomel gr. 1/10–1/4 t. i. d., is probably as good as any of the many preparations.

The Value of the Iodides

Lisser insists that the iodides occupy an important place in the specific therapy of congenital syphilis. They should be given far more frequently than is generally the case, and their mode of action and precise value should be more clearly appreciated. **The iodides should never be given without mercury or salvarsan.** The destruction of the causative organism is accomplished by the mercury and salvarsan, but the wreckage that results is swept away by the iodides. They occupy a singular rôle, therefore, in supporting and completing the work of the destroyers. The function of the iodides is to dissolve and eliminate. Although their most spectacular efficiency is demonstrated in the tertiary processes where gummas are magically made to vanish under their influence, they should likewise be used in the earlier stages of the disease, for the principle of their action remains the same, and it is at all times beneficial to aid in the elimination of the syphilitic poison.

The two commonest preparations of the iodides are the saturated solution and the combination in liquid form with mercury in the so-called "mixed treatment." When exceptional circumstances demand the use of mercury by mouth, this mixed treatment is quite satisfactory. It must be remembered that only the bichlorid or biniodid should be used in such a mixture, for the proto salts are changed by the iodides into the binary forms, making a more powerful and perhaps dangerously high dosage. If mercury is given in pill form, it should be taken an hour before meals, and the potassium iodid an hour after meals, so that the former will have left the stomach before the latter arrives.

As a routine preparation the saturated solution is very satisfactory. It should always be given in high dilutions, preferably in a large glass of milk, always after meals, as it irritates an empty stomach, and in much higher dosage than is generally prescribed. The usual dosage for adults will not be high for little children, namely 30–45 grains per day, and it is far too low for adults. Probably little good is accomplished in adults under

75 grains per day, and many cases require several hundred grains per day. So for children an initial dose of 5 grains t. i. d. is quite conservative and should be rapidly increased. Iodism is more common with small doses of potassium iodid than with enormous doses.

Malignant Syphilis

Arsphenamine plays the leading rôle in the treatment of this condition, which is characterized by rapid destruction of tissue, following marked skin ulcerations and results in the permanent formation of gummata. The process attacks chiefly the scalp, face and limbs, may affect the oral cavity and sometimes leads to bone necrosis.

A marked characteristic of malignant syphilis is intolerance to mercurial treatment. Patients easily become salivated and the drug is practically contraindicated, particularly during the early stages of the disease.

Salvarsan is usually well borne and has proved very effective. Its use as a spirocheticide is the one bright and shining feature in the treatment of this severe condition, and potassium iodid should be employed in heroic doses to aid in the absorption of gummatous infiltrations.

The hygiene of these patients must be watched carefully and they must have every advantage. The diet should be nourishing and stimulating, tonics such as quinin and iron are to be administered, and sea water bathing is advised. In addition the patient must live in the open air.

The local treatment of the ulcers consists in bathing with potassium permanganate or some equally efficient non-toxic disinfectant and dusting the sores with a pure, bland powder.

Proper hygiene, salvarsan and potassium iodid will usually prove effective in malignant syphilis.

Tertiary Lesions of the Viscera

When syphilis has invaded the vital organs of the body as the result of insufficient or improper treatment, in the form of syphilitic endarteritis, periarteritis and infiltration, vigorous

treatment must be instituted to kill the treponemata and absorp the infiltrations.

The method of procedure in these cases, according to Dr. Harlow Brooks of New York (*N. Y. State Jour. Med.*, April 15, 1916), should differ from the usual routine.

The treatment of syphilitic aortitis, aneurism and heart conditions includes at first several intramuscular injections of salicylate of mercury. Then intravenous injections of salvarsan may follow, the first being 0.3 gram and the dose is to be increased if no untoward results ensue. The course of treatment is concluded by the employment of potassium iodid in increasing doses.

The purpose of the iodid is to absorp the newly formed gummatous tissue.

Especial attention is directed to the necessity of using mercury for several weeks before commencing the arsphenamine treatment.

CHAPTER XIV

SYPHILITIC RE-INFECTION

The impression is becoming more and more firmly established that there is no such thing as a general natural immunity from syphilis. The one-time belief that one syphilitic infection brought about immunity from further infection has been broken down by cases of actual re-infection which have come to the attention of the great bulk of the syphilologists of this country from time to time.

The treatment of syphilis by means of salvarsan has undoubtedly had some effect in this connection. Under the old method of treatment it is probable that a great number of the so-called cured cases of syphilis were not cured. When one of those uncured cases showed luetic symptoms the second time it was doubtless an outbreak of the original condition. For this reason cases of re-infection were so very exceptional that the profession had good reason to believe that there was no such thing as re-infection.

We now believe that **syphilis properly treated can be cured,** and it is very apparent that re-infection does not take place until the initial infection has been absolutely cured.

A considerable number of cases of re-infection have been reported in medical literature during the last few years. General acceptance of these conditions enables the physician to judge as to positive proof of re-infection, if spirochetæ are found in a new chancre appearing in a different site from the original lesion and if the blood gives a negative Wassermann reaction. This, of course, is predicated upon the attack being seen shortly after the appearance of a lesion as well as upon the discovery in the first attack of the spirochetæ with all the presence of syphilitic lesions, such as the rash, mucous patches, or condylomata, or a positive Wassermann reaction which has not been the result of hereditary syphilis.

Major C. F. White, R. A. M. C., reports (*Brit. Med. Jour.*, Oct. 20, 1917) a series of cases in which the first attack was treated with salvarsan and mercury and a cure effected, in his belief. At a later period there was what seemed to be a re-infection, living up to the conditions heretofore mentioned, and these were treated with salvarsan and mercury and, to the best of his belief, also were cured.

He also reports another series in which the second attack did not live up to the bacteriological findings and the necessary serum tests, but he believes them, nevertheless, to have been cases of re-infection, as each one of these cases had been seen by him during both the attacks.

In the treatment of 10,500 cases of syphilis in two years, Lt. Col. Harrison saw 28 cases of re-infection. Additional cases could be quoted but these will suffice to show the physician that he must bear the possibility of re-infection in mind in the treatment of various cases of syphilis.

CHAPTER XV

THE CURE OF SYPHILIS

The day has not yet arrived for any clinician to attempt to establish a definite standard of cure of syphilis. The old method, in which the physician gave mercury and iodides over a period of years and then pronounced the cases cured, has been relegated to the discard. Sufficient time has not elapsed since the introduction of 606 to permit us to have an absolute knowledge as to the lasting effects of arsphenamine upon the spirocheta pallida. The spirochete may have resting periods; it may possess arsenical tolerance, particularly when we know that cases, which seem to have been arrested, if not cured, still continue positive. We believe that eternal vigilance is necessary in the consideration of a "cure" and, as elsewhere expressed, we should for a period of years follow up these cases and watch them carefully through the eyes of the Wassermann reaction.

The Standard of Cure of Syphilis

Oswald Dinnick, of the Royal Free Hospital of London (*Lancet*, June 21, 1919) in an instructive lecture before the London School of Medicine for Women, set forth as his belief that if, after an intensive course of arsenical medication and the continuous exhibition of mercury for two years, a patient can show two years' freedom from physical signs of disease, has a persistently negative blood serum, a spinal fluid which shows no variation from normal in either pressure, globulin content, or cellular count, and which gives a negative Wassermann in amounts of 2 c. cm.; and, if after a period of freedom from treatment, these conditions are still present and persist in spite of provocative treatment, it is justifiable, in our present state of knowledge, to presume this patient cured.

Finally, should this patient subsequently develop a fresh chancre, at a site differing from the first, this would be a re-infection, and would prove our contention. For syphilis does not confer immunity, and the real interpretation of all alleged immunity is that the so-called immune person is an active syphilitic.

Wechselmann, in his *Salvarsan Therapy*, Volume 2, page 110, sets forth conditions of cure which are accepted by many persons as authority. According to him, cure is effected when the patient is free from symptoms of the skin, mucous membrane, and all inner organs; when his blood serum no longer shows a positive Wassermann reaction; when his lumbar puncture shows no alterations, and if this absence of all positive signs, especially the negative Wassermann and the negative lumbar puncture, remains permanent upon most careful control for a certain period of time.

Wechselmann says that this particular period is generally accepted as one year, although this is not absolute. He advises the taking of the blood for the Wassermann at from two to four-month intervals and that a spinal puncture should be made at less frequent intervals.

We believe that Wechselmann's time limit is too short and are much more inclined to accept Dinnick's views that the patient should show two years' freedom from physical and serological signs.

Prevention of Infection of the Operator

Some physicians exercise little or no precaution against infecting themselves while administering arsphenamine and neo-arsphenamine.

It must be borne in mind that the blood of all syphilitics is infectious, that of persons in the primary and secondary stages being more capable of conveying the infection than that in tertiary and latent stages.

It is agreed that the chancre and the mucous patch are much more fertile fields of infection than the blood, but as all these sources readily transmit the treponemata, the physician should protect his hands with rubber gloves and as a double precaution

he should employ collodion about the finger nails in the event of the presence of a hang nail or an abrasion.

Penetration of the operator's hand or finger by a used salvarsan needle should be followed by an immediate laying open on the part, after first shutting off the blood supply, and the application of pure phenol. The introduction of an injection of arsphenamine or neoarsphenamine is also advisable on account of its prophylactic action, as elsewhere set forth.

The Care of Arsphenamine Needles

Niceties in technic in arsphenamine administration are essential. Little matters of detail may cause a change from trouble to comfort. Arsphenamine needles need as much care as the other parts of salvarsan's administrative apparatus, but they are too often neglected. A glance through the bore of a used needle will likely reveal a dirty lumen and the residue in the bore when examined will be found to be a black mass of unknown composition, which has no place in any aseptic operation.

The writer has kept needles clean by the use of a good metal polish and a copper wire a little larger than the stylet accompanying the needle. The wire should fit the bore of the needle closely. Part of the wire is dipped in the metal polish and is drawn back and forth through the needle several times. If the wire is then wiped off on a piece of gauze a black deposit will be observed.

The clean wire is again immersed in the metal polish and the operation is repeated until no deposit is left on the gauze. The bore of the needle should be as clean as the bore of a rifle.

After administering salvarsan it is our custom to boil the needle, run alcohol through it and then cover it with I D L, an Irish moss preparation, which prevents rusting. It may also be kept in oil.

Arsphenamine needles must be very sharp, with a short bevelled edge, to prevent wounding of the vein. We formerly sent needles to an instrument maker to be sharpened, but of late have personally utilized a piece of carborundum for the purpose. By so doing the physician can always have a sharp needle at his

command, with the kind of point which his experience demonstrates is best.

In a discussion of the care of needles, the type of needle may be mentioned.

A number of syphilologists have had special needles made embodying ideas of their own, but most physicians use the needle they first employed when giving intravenous injections.

After trying the various types on the market, we have adopted the Fordyce and use it exclusively.

Its particular advantage is the shank, which enables the operator to obtain such a firm grasp that no sudden movement on the part of the patient can shake it out of his hand.

This shank also permits the physician to pursue a rolling, elusive vein, which may not have been properly fixed between the thumb and forefinger of the other hand, without making a second entrance through the skin.

Hygiene for Syphilitic Patients

No alcoholic liquors should be ingested.

The use of tobacco, either by smoking or chewing, aggravates those cases in which mucous patches are present in the mouth.

Tepid baths should be taken daily, if no eruption be present, followed by a brisk rub. A hot bath should be taken every two or three days. Sometimes a hot water shower, followed by a cold one, is of benefit. Turkish baths may be taken once or twice a week, if no active skin troubles are present.

The teeth should be brushed in the morning, after meals, and upon retiring, and a cleansing mouth wash will add to the patient's comfort.

The patient should sleep alone.

He should use his own dishes and table cutlery, towels, tooth brush, brushes, combs, shaving utensils, pencils, scissors, etc.

He should kiss no one and sexual intercourse is strictly interdicted for the first year of the disease or during a relapse.

During the presence of oral mucous patches he should keep his fingers out of his mouth and be particular that his saliva does not come in contact with any one or with anything in use.

He should wash his hands very frequently and always after touching his genitals.

Dietary for Syphilitic Patients

In the treatment of lues it should be remembered that the patient is suffering from a constitutional disease, that he demands special food and that his particular symptoms necessitate treatment as they arise.

The following dietary is suggested:

The Patient Can Have

Soups, all except tomato.

Fish.—All fresh fish, boiled, baked, or broiled. Raw oysters, scallops, lobsters and clams.

Meat.—Beef, mutton, roasted, boiled or broiled; poultry; game; veal, lamb chops or cutlets; eggs, soft boiled, scrambled, poached, raw or in omelettes.

Farinaceous.—Cracked wheat, oatmeal, mush, sago, tapioca, rice, hominy, barley, marcaroni, vermicelli, whole-wheat bread, stale or toasted wheat bread, brown bread, milk toast, corn bread.

Vegetables.—Green peas, string beans, parsnips, turnips, spinach, cauliflower, mushrooms, celery, lettuce, asparagus, sweet potatoes, white potatoes in moderation, preferably baked.

Desserts.—Custards, rice or cornstarch puddings, blanc mange.

Drinks.—Water, plain or aërated, cocoa, chocolate, milk, koumiss. A limited amount of coffee may be given when no active symptoms are present.

The Patient Can Not Have

Any fried foods, or pork cooked in any way.
Any sour, acid, spicy or peppery foods.
Any canned, salted, pickled or preserved meat or fish.
Any alcoholic drinks or tea.
Any pastry.

The patient should be instructed

To eat animal food at every meal and to eat more animal than starchy food.

When Can the Syphilitic Patient Marry?

Nearly forty years ago Fournier of Paris, in his *Syphilis et Mariage*, set down these governing rules for the marriage of syphilitic patients:

a. Absence of actual specific lesions.
b. Advanced age of the infection.
c. A certain period of absolute immunity.
d. Non-menacing character of the disease.
e. Sufficient specific treatment.

Finger of Vienna in 1896 specified that five years should intervene between the times of infection and marriage and that three years should intervene between the last syphilitic manifestation and marriage, there having been systematic treatment of the disease, with an energetic course of mercurial treatment preceding the marriage ceremony.

Dr. Joseph Lewi, who for fifty years practiced medicine in Albany, N. Y., at a time long before arsphenamine was brought to the attention of the medical world, advised as follows:

"No man or woman ever afflicted with syphilis has a right to marry until three years after all symptoms of the disease have disappeared. In the meantime and for a period of three years, the mixed treatment (one thirty-second of a grain of corrosive sublimate and ten grains of iodid of potassium) should be given such patients three times a day for a period of twenty days at four different periods of each year."

Observations, extending over a period of seventy years, of cases coming under the care of Dr. Lewi and his sons, who cooperated with and succeeded him in practice, show that where the treatment was followed as above outlined, the after-effects on progeny were limited to cases of premature birth and of abortions in first and second pregnancies, and that other complications were negligible.

In the light of our present knowledge the physician should not give his consent to the marriage of a syphilitic patient until the provocative injection, after repeated Wassermanns, of blood and spinal fluid have demonstrated that the spirochetæ have been absolutely eliminated from the system. A man with a positive Wassermann, even though it be caused by an aortitis or a lesion of the spinal cord, should not marry or endeavor to procreate.

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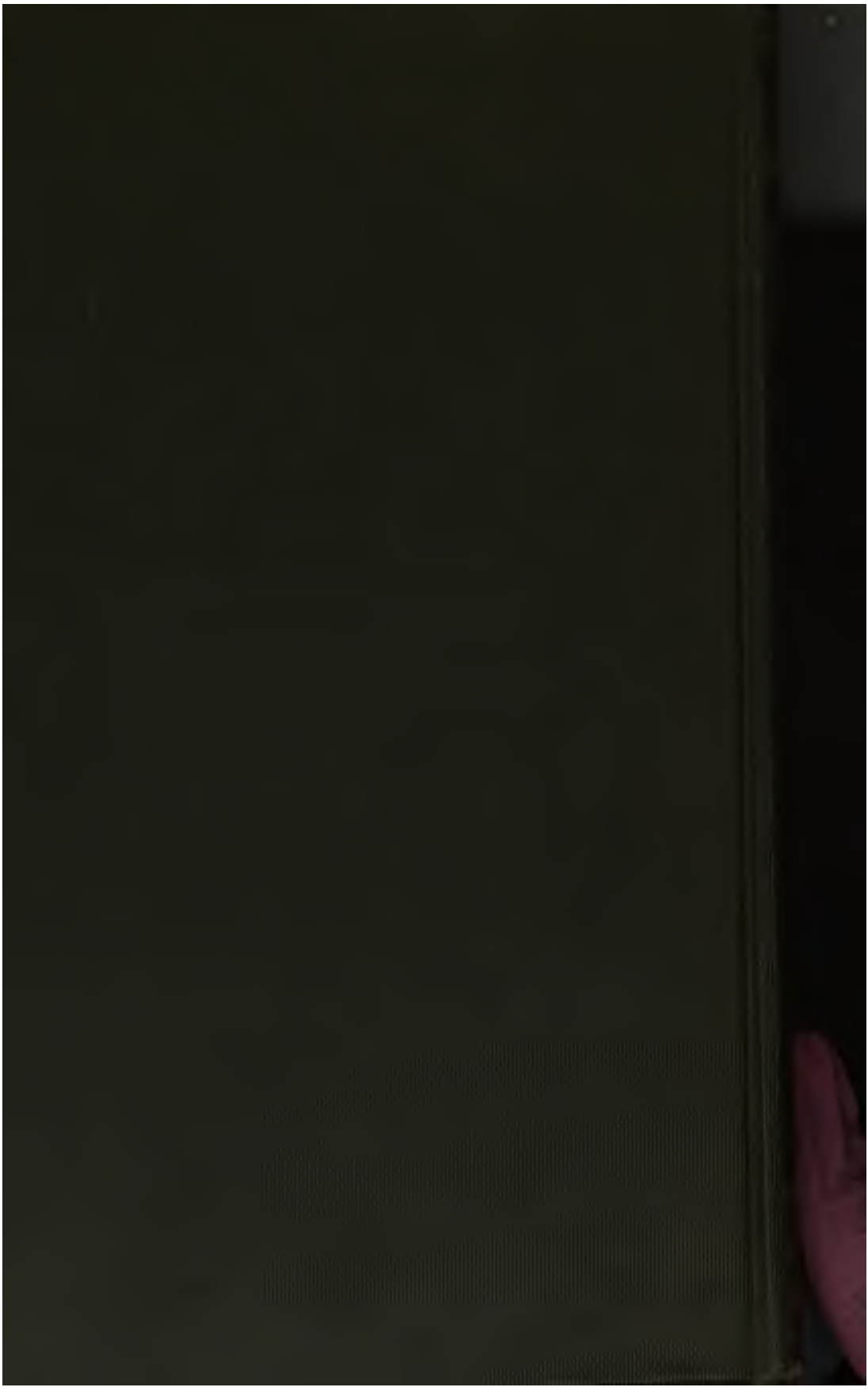
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